CONGENITAL PERICARDIAL DEFECTS

BY

SYDNEY SUNDERLAND AND R. J. WRIGHT-SMITH

From the Department of Anatomy and Histology, University of Melbourne, and the Department of Pathology, Royal Melbourne Hospital, Australia

Received October 10, 1944

Congenital pericardial defects are among the most uncommon of reported cardiac anomalies. In 1925 Moore was able to find 64 references to pericardial defects, but a detailed re-examination of the records by Southworth and Stevenson in 1938 reduced the number of confirmed cases in man to 52 and 7 of these occurred in monsters. They added another case to this series, and in a footnote to their paper referred to the case described by Dahl (1937) in which, however, a traumatic or pathological basis for the defect could not be definitely excluded: their review did not include Ladd's (1936) case. The purpose of this paper is to record the findings in two additional specimens. One is of especial interest in that the defect was directly responsible for the death of the patient. Such a result has been recorded on one previous occasion only.

It is not proposed to review the literature in any detail since this has already been comprehensively covered in excellent papers by Moore (1925), de Garis (1934), and Southworth and Stevenson (1938).

Reports of Two Cases

Case 1. *J. E. S.*, a boy, aged 2 years 2 months, was apparently healthy. He had been playing with an older boy when he complained of distress and ran to his mother holding the back of his head. He was rested, but still showed distress, and five hours after the onset refused his evening meal. A few hours later he became very restless and vomited. Fourteen hours after his first complaint, he suddenly collapsed and died. He did not receive any medical attention. An autopsy was performed eight hours after death. The body was that of a well-nourished male infant, well developed for his age. There were no external marks.

A large part of the parietal layer of the pericardial sac was absent (Fig. 1). The parietal layer present extended to enclose completely the right atrium and the greater part of the right ventricle. Anteriorly it showed a free, well-defined, constricted and rather rigid edge which crossed the sterno-costal surface of the heart from the root of the pulmonary trunk above to the inferior margin below, at a point well to the right of the apex. This free edge was situated to the right of the anterior interventricular sulcus and the interventricular branch of the left coronary artery. Inferiorly it was attached to the central tendon of the diaphragm between the inferior vena cava on the right and the line of the inferior interventricular sulcus, with its contained branch of the right coronary artery, on the left. Posteriorly it crossed the basal surface of the heart to the left of the pulmonary veins to reach again the left face of the root of the pulmonary trunk. The left ventricle and left auricle projected through this rigid orifice, the constricted edge of which had deeply grooved the surface of the heart. The mediastinal pleura on the left side below the hilum of the left lung also showed a large deficiency so that the left ventricle lay free in the left pleural cavity touching the median surface of the lower lobe of the left lung.

The surface and muscle of the right atrium were pale. The surface of the right ventricle was pale; the muscle was also pale, except at its apex, where it showed congestion and

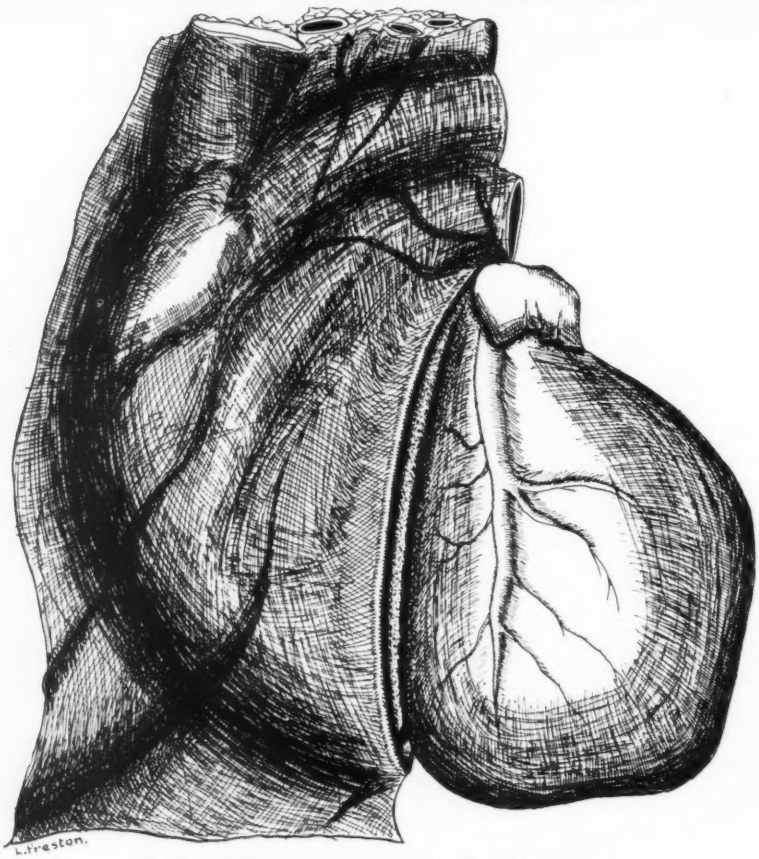


FIG. 1.—The heart and pericardium in Case 1 (see text).

hæmorrhage. The surface of the left ventricle was dark red and hæmorrhagic with many small focal hæmorrhages. The muscle of the left ventricle showed some hypertrophy. It was dark red in colour and at the base and apex there were large areas of hæmorrhage in the muscle tissue. The surface and muscle of the left atrium were very congested. The coronary sinus and great cardiac vein were distended with dark fluid blood. The cavities on the right were normal in size and contained red clot. On the left side, both the atrium and ventricle were dilated and contained red clot and fluid blood. The endocardium of the left ventricle showed some recent small hæmorrhages. The valves were normal. The foramen ovale was closed and there was no deficiency in the interventricular septum. The ductus arteriosus was patent though the lumen was constricted in the centre to about 2 mm. in diameter. The aorta and its branches were normal.

The right pleural sac and the diaphragm were normal. The lungs were large and pale-red and showed a fine œdema in all parts. The bronchi and trachea were pale and filled with fine white froth. The thymus was not enlarged and the substance was pale-red and firm. The larynx, pharynx, and thyroid were normal. The alimentary tract and peritoneum were normal and the viscera showed no congenital abnormality. The liver was moderately congested and firm. The spleen was pale-red and soft. The pancreas and suprarenals were normal. The kidneys were congested and firm. The ureters and bladder were normal. The testes had not fully descended being just below the subcutaneous inguinal ring; they showed a normal structure. The bones of the skull were normal. The membranes of the brain were congested, and the brain was rather pale and firm, but showed no abnormality.

Case 2. *L. C. D.*, a man, aged 61 years, had had a stroke some two-and-a-half hours before admission to hospital, and could give no clear history. Examination revealed a well-nourished man showing deviation of the head and eyes to the right with tremor and flexion of the right arm and paralysis of the left arm and leg. He was treated as a case of cerebral thrombosis.

The temperature was 97·8° F., the pulse rate 70, and the respiratory rate 20. The blood pressure was 170/100. The apex beat of the heart was in the left fifth intercostal space six inches from the mid-line. There was no right cardiac dullness and the sounds were regular and clear. Examination of the lungs and abdomen showed no abnormality. After some days moist sounds developed at the base of both lungs, and this was accompanied by elevation of the temperature and pulse rate. There was no improvement in the paralysis and the patient became incontinent. Six days after admission there was a sudden, rapid rise in the pulse rate and examination of the heart showed a " to and fro " murmur at the pulmonary area which was thought to be a friction rub. The systolic blood pressure fell to 150; the diastolic pressure remained at 100. The temperature at this stage was 100·4° F., the pulse rate was 156, and the respiratory rate 26. The patient died eight days after admission. An autopsy was performed eight-and-a-half hours after death.

There was no pericardial sac in the true sense of the word (Fig. 2). The parietal layer was entirely deficient over most of the anterior surface of the heart, the whole of the apex, and much of the diaphragmatic and basal surfaces. It presented a free, loose margin, which was cord-like

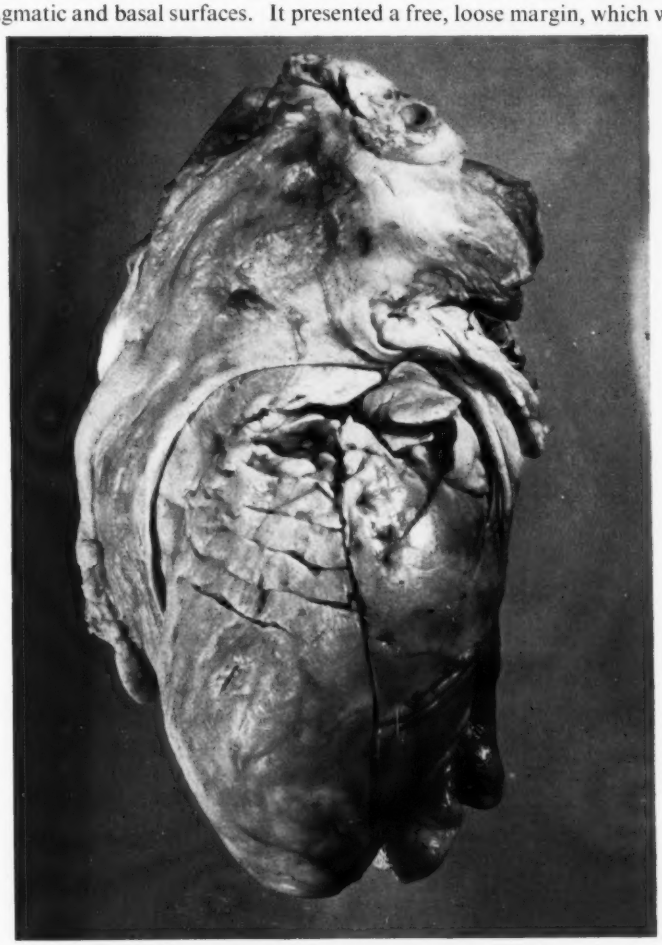


FIG. 2.—The heart and pericardium in Case 2 (see text).

and smooth. Anteriorly the free margin appeared in the interval between the left auricle and the pulmonary trunk from which position it swung transversely to the right across the pulmonary trunk, the aorta, and the right coronary artery. It then curved downwards and crossed the sterno-costal surface of the right atrium, to the right of, and parallel to, the atrio-ventricular groove and the right coronary artery, to reach the right margin of the heart inferiorly. Turning round this margin it continued to the left, immediately anterior to the inferior vena cava, and was here attached to the central tendon of the diaphragm. It then ascended obliquely and to the left across the basal surface of the heart. On reaching the atrio-ventricular sulcus and the coronary sinus it accompanied these upwards to enter, from behind, the interval between the pulmonary trunk and the left auricle. Thus the greater portion of the heart was uncovered by parietal pericardium. Where present, this sheet was joined to the epicardium by scattered adhesions which prevented the free separation of the two structures. The parietal pleura was complete on both sides. The heart was large. It weighed 567 g. (20 oz.). There was some hypertrophy of the left ventricle.

The coronary orifices were patent. The coronary arteries were thickened and atheromatous and showed patchy calcification. All branches were grossly narrowed. The left descending branch and the middle portion of the right coronary artery were completely occluded. The epicardium, apart from adhesions, appeared normal. The muscle of the left ventricle showed coarse fibrous scarring in the inner and middle layers. The endocardium of the left ventricle was white and densely fibrous. All cavities were dilated. The papillary muscles on the left side and the interventricular septum showed fibrosis. The valves were normal. The foramen ovale and the ductus arteriosus were closed. The aorta was large, thick-walled, and markedly atheromatous.

The lungs were large and the right lung presented four well-defined lobes. There was some early bronchopneumonic consolidation at both bases. The cerebral arteries were thickened and atheromatous and the basilar artery contained some pale thrombus. The brain showed large areas of softening and necrosis in the white matter of the right hemisphere. There were numerous small hæmorrhages in both hemispheres and in the pons. The other organs were normal.

Development of the Pericardial Cavity

The normal development of the pericardial and pleural cavities will be briefly outlined before proceeding to a discussion of the embryological basis of these defects.

During the first weeks of development, when the embryo is but 1·5–2·0 mm. in length, irregular cavities appear in the mesodermal substance of the embryo, and these, by their enlargement and coalescence, form the primitive pericardial, peritoneal, and pleural cavities. The pericardial cavity is outlined by the fusion of a series of spaces that develop in the mesoderm surrounding the endothelial anlage of the developing heart to permit the effective functioning of that organ. In the lateral mass of body mesoderm the peritoneal cavity is similarly formed about the developing gut to permit intestinal movements.

A wedge of mesoderm, directed transversely across the embryo, is left interposed between these two cavities. This is the septum transversum and it contains the developing liver and the termination of the umbilical and vitelline veins. The septum does not, however, effect a complete separation between the two cavities, for these communicate dorsally, on either side of the mid-line, by the paired longitudinally-disposed pericardio-peritoneal canals. The developing lung buds ultimately herniate into these canals which fold about them, as development proceeds, to form the pleural sacs. With the formation of the head-fold the pericardial cavity comes to lie on the ventral side of the primitive pleural sacs.

The final stages of cœlomic differentiation are initiated at about the fifth week, when each pleural sac is sealed off from the pericardial cavity above and the peritoneal cavity below. Only the mechanism involved in the former process is relevant to this discussion. The separation is effected in the following manner. On each side the ductus Cuvieri establishes contact with and compresses the pericardio-peritoneal canal as it passes from the body wall

to the heart. The pressure exerted by the vessel results in the formation of an elevation, the pulmonary ridge, which narrows the lumen of the canal. The most cranial portion of this ridge of tissue is intimately related to the opening between the pleural and pericardial cavities, and here it forms a valve-like membrane, the pleuro-pericardial membrane.

Some believe that pressure exerted by the growth of the ductus Cuvieri is alone responsible for closing the communication between the two cavities, while others claim that the communication is only partially constricted by the venous channel, and that its closure is finally completed by the active enlargement of the pleuro-pericardial membrane. It is difficult to assess the respective values of these two factors in effecting the closure, but it seems certain that both operate either in succession or coincidentally. It must not, however, be forgotten that, as growth proceeds and the pericardial and pleural cavities expand, the connection between the two, being an area of inactive growth, is gradually reduced to a minute foramen. It is upon this narrowed opening that the factors indicated above operate. The following, then, may be regarded as the essential factors responsible for the closure of the communication: (1) the relative reduction in the size of the opening consequent on the more active growth of neighbouring structures; (2) the active growth within the pleuro-pericardial membrane; and (3) the continued enlargement of the pleuro-pericardial membrane under the influence of the duct of Cuvier.

Interpretation of the Defects

Few attempts appear to have been made to account for the abnormality (Keith, 1907; Perna, 1909; Risel, 1911, 1912; Plaut, 1913; McGarry, 1914; Watt, 1931; and de Garis, 1934). It is generally accepted that the defect represents a persistence of the pleuro-pericardial foramen, but opinions are divided concerning the mechanism operating to prevent its normal closure. An examination of the records shows that the condition is almost exclusively left-sided. In one monster the defect was right-sided, and in another it was thought to be bilateral. Excluding the monsters, there was one human case in which the defect was possibly on the right and Moore (1925) has described a defect on this side in the dog. The defect varies in size from a small opening to one in which the entire left side of the pericardium is absent, thereby leaving the heart and lung occupying a common serous cavity. Any explanation advanced to account for the abnormality must satisfy these morphological features.

Keith (1907) claims, on the basis of observations on two specimens, that the pericardial defect " had been produced by the lung bud growing within and expanding the communication between the pericardium and pleura, for that communication lies immediately ventral to the point at which the lung bud appears. The condition should be described as dilatation of the pleuro-pericardial foramen." Keith, however, fails to explain why the lung bud herniates into the foramen and not into its normal position, or why the defects are almost exclusively left-sided. Though such an explanation as the one offered might conceivably account for the condition in his two specimens very few of the other recorded defects could be satisfactorily accounted for in this way. Perna (1909) and later Plaut (1913) advanced the theory that persistence of the communication is the result of the arrested development of the pleuro-pericardial membrane consequent on the premature obliteration of the left duct of Cuvier. On this basis, however, all defects should be left-sided. Moore (1925) also inclines to this view though the defect which he described was on the right side.

Risel (1912) disagreed with Perna's (1909) explanation on the grounds that there were extensive combined defects in the three monsters described by him (Risel) and that in one of them the pericardial defect was bilateral. He was content to attribute the defect solely to unspecified disturbances in general cœlomic differentiation occurring early in development. Such an explanation is too vague to be of value in explaining the majority of the defects recorded.

McGarry (1914) suggests that " the cells lining the cœlomic space, may at some period be

particularly sensitive, and abnormal conditions occurring at this time, would result in disturbances, either an over-production or an under-production, of the serous derivatives " and attributes to this factor the lack of development of the pleuro-pericardial membrane. The abnormal conditions, however, are unspecified and he attempts to explain the almost exclusive incidence on the left as being due to the greater tension exerted on the pleuro-pericardial membrane by abnormal influences, induced by the asymmetry and rotation of the liver, which arrest its development. No evidence is advanced in support of this assumption.

Watt (1931) explains the defect as the result of the arrested development, from unspecified causes, of the pleuro-pericardial membrane—the subsequent enlargement of the communication being due to the presence of the heart or lung.

According to de Garis (1934) it is the heart that obstructs the closure of the foramen. He claims that the expansion of the heart tube to the left, which takes place during its enlargement and folding, is occasionally sufficiently great to prevent the pericardial, the pleural, or both these components of the pleuro-pericardial membrane, from growing forwards in their normal position. On this basis he explains all degrees of left-sided pericardial defect either with or without free communication between the pericardial and left pleural sacs. Though he cites as confirmatory evidence the fact that in many cases the heart is enlarged, elongated, or both, he maintains that " failure to find the adult heart abnormal in size or shape would not preclude the possibility that at a critical stage of development, when the pleuro-pericardial membrane grew ventrally and cranially, this growth was inhibited by the left-sided extension of the heart, which latter may or may not have been enlarged."

Thus all, with the exception of Risel, agree that the basis of the defect is obstruction of the normal development of the pleuro-pericardial membrane. Of the various theories advanced those of Perna (1909), Plaut (1913), and de Garis (1934) conform most closely to known embryological stages of development though they fail to account for those rare but confirmed cases in which the pericardium has been deficient on the right. Moreover, if the defect be attributed solely to the failure of the pleuro-pericardial membrane to develop, the pleural and pericardial cavities should remain in continuity in every case: but this is not always so. de Garis explains cases in which the pericardium alone is incomplete on the basis that the enlarging heart obstructs only the development of the pericardial aspect of the membrane.

There would appear, however, to be another factor operating in the production of these defects. The pericardium is obviously stretched as the pericardial cavity enlarges in order to accommodate the developing heart. Any opening in that enveloping sheet which is present when this process of stretching and enlargement sets in will be exaggerated unless factors normally leading to its closure operate at a much greater rate than that at which the opening is stretched. Consequently, if the foramen is to escape involvement when the pericardium is stretched it must close before the heart actively and rapidly enlarges. During the early stages of development it is conceivable that, in certain instances, the pleuro-pericardial foramen may be either unduly large, and/or its closure delayed or prevented, owing to (1) the arrested development or absence of the pleuro-pericardial membrane; (2) the failure of the membrane to grow at the rate required to close the foramen in time; (3) the absence or diminished effect of the differential growth factor which normally leads to its narrowing; or even (4) the direct influence of the enlarging heart as suggested by de Garis. Under these conditions the foramen is slowly widened as the pericardium is stretched by the enlarging heart and unless the factors responsible for its closure can, by their accelerated growth, make up lost ground it persists as a defect. Though the heart is entirely inside the pericardium in many of these abnormal cases, the defect present is obviously much larger than the original communication connecting the pericardial and pleural cavities. This lends support to the belief that the stretching to which the pericardium is subjected during development plays a significant role in maintaining and enlarging the foramen. Absence of the pleuro-pericardial membrane or obstruction to the closure of the pleuro-pericardial opening, acting singly or together, could hardly lead to an

increase in size of the original communication. If, however, the heart is unduly large, which it appears to be in approximately half the cases, then direct pressure on the foramen by the enlarged heart could assist not only in keeping it open but also in actively dilating it.

The pericardial or both aspects of the pleuro-pericardial membrane may be involved in the manner indicated, thereby imparting to the defect those varieties in which the pericardium alone is defective or in which the pericardial and pleural cavities are in continuity. Moreover, during development both the right and the left pleuro-pericardial openings may be subjected to abnormal influences of the type described, which will result in pericardial defects. Naturally, however, such abnormalities will predominate on the left since there are additional factors operating on that side (obliteration of the duct of Cuvier, enlargement of the heart to the left, etc.), which may delay or prevent the closure of the foramen until the rapid growth of the heart can influence it.

The final size of the defect is determined by the original size of the foramen, the extent to which it is stretched by the enlarging heart, and the extent to which the factors attempting to close it are successful. The size of the defect at the time when the heart first begins to enlarge will also influence the degree to which that organ will project beyond the confines of the pericardium. The defect may never, at any stage, be sufficiently large to receive any portion of the heart that continues to develop entirely within the pericardium. This latter structure then shows, when development is completed, a defect of varying size, which is never sufficiently extensive to permit the heart to herniate through it when it expands physiologically or enlarges pathologically. On the other hand the foramen may be of such dimensions in the initial stages that the heart can protrude through it either partially or entirely. Under these conditions the organ may proceed to develop outside the pericardium in a common serous cavity with the left lung. The foramen is then progressively enlarged about the heart as it develops. Again, the defect may be of such a size when development ceases that, though the heart does not normally protrude through it, it may do so in the event of any enlargement produced pathologically or under conditions of extreme stress and exertion. If the heart be driven forcibly through the aperture in this way it may be constricted by the margins in such a manner as to affect adversely cardiac efficiency—in Boxall's case and the first case reported here the constriction was sufficiently severe to cause death.

Such a theory as that outlined accounts for both right- and left-sided defects, for the overwhelming predominance of the latter, and for all types and degrees of deficiency. The factors that appear to be responsible for the defect, acting either singly or in combination, may be conveniently summarized as follows.

(1) The normal stretching of the pericardium which takes place coincidentally with the enlargement of the heart.

(2) Premature and/or abnormal enlargement of the heart which precedes the closure of the pleuro-pericardial foramen. Projection of the heart through the opening at this stage effectively prevents any possibility of closure at a later date.

(3) An abnormally large foramen which is not fully closed when the heart and pericardium start to enlarge.

(4) Delayed or non-closure of a normal pleuro-pericardial foramen which is subsequently enlarged as the pericardium stretches to accommodate the developing heart. This arrested development may be due to: (*a*) defective formation of the pleuro-pericardial membrane as a result of premature obliteration of the duct of Cuvier or some other unidentified influence; (*b*) direct obstruction by the enlarging heart; or (*c*) failure or diminished activity of the differential growth factor by which the connection between the pleural and pericardial cavities is gradually reduced to a minute foramen.

(5) Failure of a membrane, whose development has been delayed, to grow sufficiently rapidly to close a defect which is being slowly extended as the pericardium expands to contain the enlarging heart.

Clinical Aspects of Pericardial Defects

Apart from purely embryological considerations the clinical features associated with these defects are not without interest and may be briefly reviewed.

Side. Attention has already been directed to the almost exclusive incidence on the left. Both specimens reported in this paper were left-sided.

Type. Moore (1925) has classified the reported cases into the following three groups.

Group I. Those in which the heart and left lung occupy a common serous cavity. He records an incidence of 60 per cent in his series and Southworth and Stevenson (1938) one of 76 per cent in theirs.

Group II. Those in which there is only a foramen between the pericardial cavity and left pleural sac. He records an incidence of 21 per cent and Southworth and Stevenson (1938) one of 24 per cent. Both specimens reported in this paper would be included in this group though in the second case the defect involved the pericardium only.

Group III. Those in which there is either no trace of a pericardium or only rudiments thereof. He records an incidence of 19 per cent. Southworth and Stevenson (1938) believe that such a condition has never been conclusively demonstrated. This latter view is shared by the authors.

Associated Congenital Anomalies. Associated defects were multiple and extensive in the seven monsters. In six of the recorded series, associated anomalies in other organs were represented as follows: heart (2), lungs (1), pleural cavity (1), peritoneum (1), and kidney (1). However, as Southworth and Stevenson (1938) point out, the records of many cases are incomplete in that they contain references only to the cardiac condition. Associated defects were present in the two cases described in this report. In the first case the ductus arteriosus was patent and in the second the right lung was divided into four well-defined lobes.

Sex. From the reports that contain references to the sex it appears that the condition is approximately three times as common in males as in females. Both cases described in this report were males.

Influence on Expectation of Life. Southworth and Stevenson (1938), on the basis of a comparison of the mean age at death for the series of reported anomalies with the mean age at death for the United States area of registration for a given year, conclude that " the anomaly has no appreciable influence on life expectancy." In only two cases, that of Boxall and *Case I* in this paper, could death be attributed to the defect, and in neither was the condition diagnosed during life. Boxall's (1887) case was an adult in whom death occurred three days post-partum. Autopsy revealed a left-sided pericardial defect through which the heart had herniated and become strangulated. Death occurred suddenly with symptoms suggestive of a pulmonary embolism. It was suggested that changes in intrathoracic pressures following delivery were responsible for the fatal complication, but it is difficult to comprehend how this could have occurred three days after delivery when the heart was no longer subjected to the severe stress of labour.

Size of the Heart. From the limited number of cases containing a reference to the size of the heart, it would appear that, excluding those cases in which the enlargement was due to associated cardiovascular disease, the heart was enlarged in about 50 per cent of the cases.

Symptoms. Cardiac symptoms that could possibly be attributed to this abnormality were present in only three cases; there was a mild angina in two, while in the third adherent pericarditis was suspected during life and death was due to unexplained cardiac failure. The association between symptoms and defect in these three cases cannot, however, be regarded as conclusive. From an examination of the data contained in the case histories it may reasonably be inferred that pericardial defects are rarely the cause of cardiac symptoms. No symptoms directly attributable to the pericardial defects were present in the two cases here described.

Complications. It is interesting that in the two cases in which death could be attributed

to the abnormality death was due to herniation of the heart through the defect, this being followed by strangulation. This, however, must be considered a rare event. On occasion, when the heart is partially outside the pericardium, pressure from the firm rim of the aperture may press on one or other of the coronary vessels and obstruct it. No such factor was operating in the second case described in this report. Though the heart is enlarged in 50 per cent of the cases there is nothing to suggest that this enlargement is due to the defect. Attention has frequently been directed, however, to the fact that continuity between the pleural and pericardial cavities exposes the heart to pulmonary infection (Abbott, White, Southworth and Stevenson, and others). There was a high incidence of pleuro-pericarditis in the recorded cases, and in 27 per cent death was due to pulmonary infection complicated by pleuro-pericarditis.

Diagnosis. Ladd (1936) observed the anomaly in a child aged two during the repair of a congenital diaphragmatic hernia. Dahl's (1937) patient developed a pneumopericardium during the establishment of a left pneumothorax which, according to him, could only be explained on the basis of a defect in the pericardium. Whether this was congenital or due to disease or trauma could not be ascertained. Excluding these cases the condition has never been recognized during life though Southworth and Stevenson (1938) carried out a detailed examination and investigation of the cardiac condition in a patient who was found to have a pericardial defect post-mortem. They conclude that " although the diagnosis is probably impossible in cases where the defect is represented only by a foramen, in those where there is a common cavity on the left the diagnosis may be suspected from (1) unexplained displacement of the heart to the left, and further confirmed if, in the absence of adhesions, there is (2) abnormal mobility of the heart. Unexplained cardiac enlargement (3), if present, would be further evidence in favour of the diagnosis, though its absence would not be significant." These conclusions are in general agreement with those reported by Maude Abbott (1927).

Summary

Two cases in which post-mortem examination disclosed a congenital pericardial defect have been described. In neither case was the condition diagnosed or suspected during life. In one it was directly responsible for the death of the patient.

The normal development of the pericardial cavity has been briefly outlined.

The various theories advanced to account for the defect have been discussed and the limitations of each indicated. An alternative explanation has been advanced to account for all the morphological features displayed by the defect.

The clinical features of the condition have been briefly reviewed.

References

An extensive bibliography has not been included. Such is provided in the papers of Grant, de Garis, Moore, and Southworth and Stevenson.

Abbott, M. (1927). Congenital Cardiac Disease, in Osler's *Modern Medicine*, Vol. 4. Philadelphia.
Boxall, R. (1887). *Trans. Obst. Soc. Lond.*, **28,** 209.
Dahl, E. (1937). *Med. Rev. Bergen*, **54,** 312.
Grant, R. T. (1926). *Heart*, **13,** 370.
Keith, A. (1907). *J. Anat. Physiol.*, **41,** 6.
de Garis, C. F. (1934). *Anat. Rec.*, **59,** 69.
Ladd, W. E. (1936). *New Eng. J. Med.*, **214,** 183.
Moore, R. L. (1925). *Arch. Surg.*, **11,** 765.
McGarry, R. A. (1914). *Anat. Rec.*, **8,** 43.
Perna, G. (1909). *Anat. Anz.*, **35,** 323.
Plaut, M. (1913). *Z. Path.*, **12,** 141.
Risel (1911). *Dtsch. med. Wschr.*, **37,** 2,405.
—— (1912). *Verhandl. dtsch. path. Gesellsch.*, **15,** 379.
Southworth, H., and Stevenson, C. S. (1938). *Arch. intern. Med.*, **16,** 223.
Watt, J. C. (1931). *Arch. Surg.*, **23,** 996.
White, P. (1931). *Heart Disease*. New York.

CASUAL AND BASAL BLOOD PRESSURES

IV. THEIR RELATIONSHIP TO THE SUPPLEMENTAL PRESSURE WITH A NOTE ON STATISTICAL IMPLICATIONS

BY

F. H. SMIRK

From the Department of Medicine, University of Otago, New Zealand

Received September 18, 1944

In an article entitled *Casual and Basal Blood Pressures in Essential Hypertension* (Alam and Smirk, 1943, b), two statements were made in the discussion upon which it is desired to offer further evidence.

1. " It seems desirable to regard the casual blood pressure as made up of two parts, namely, the relatively stable basal blood pressure and a variable supplemental pressure. The supplemental pressure is the part of the casual blood pressure that is elevated as the result of the patient's physical, mental, and emotional activity, chiefly the latter; the elevation of the basal blood pressure in essential hypertension requires some other explanation." This statement that the supplemental pressure varies and the basal pressure is relatively constant refers, as is indicated in the last sentence, to the individual and not to comparisons between different individuals. Measurements of the basal pressure, whatever technique be adopted to obtain it, aim at removing these known causes of variation and at measuring a pressure that has been obtained under standard conditions of mental and physical rest. There is a high probability, therefore, that basal readings obtained under standard conditions will be more constant for the individual than casual readings taken under a variety of conditions. This has now been shown, experimentally, by Kilpatrick.

2. " The lability of the blood pressure in a case of essential hypertension may be judged by the degree of difference between the casual and basal pressures." In Fig. 4 of the paper referred to above the relationship of this difference, which we call the supplemental pressure, to the casual and basal pressures is set out graphically. It was suggested by the authors that the patients with the higher supplemental pressures are in general those with higher casual blood pressures, but their basal pressures are no higher than those of essential hypertension patients with lower supplemental pressures.

The object of the present paper is to describe some further observations that confirm the views previously expressed as to the relationship of the basal and supplemental pressures in essential hypertension, to study this relationship in health, to rediscuss the conditions under which the basal blood pressure should be measured, and to make reference to the significance which this conception has in relation to the statistical analysis of the ordinary casual (clinical) readings of the blood pressure. The opportunity is taken of referring to a comment by the editor of the *British Heart Journal* upon a statement in a previous paper (Alam and Smirk, 1943, b), which was to the effect that our results shown in Fig. 4 did not seem to support one of our conclusions.

The basal and supplemental pressures have a practical importance which should make their separate determinations a matter of clinical routine in certain classes of patient.

METHOD

Measurements of the casual and basal blood pressures were made in healthy men and in patients with essential hypertension by the method described by Alam and Smirk (1943, a).

The results together with some of those already published are analysed statistically. Experiments were made also on the effect of modifying the conditions under which the basal blood pressure is measured.

A method for determining the basal blood pressure has been recommended by committees appointed by the Cardiac Society of Great Britain and Ireland and the American Heart Association. In essence their recommendation is that the blood pressure should be measured after preparation of the subject similar to that used for basal metabolic rates. Alam and Smirk provided evidence of the need for a deliberate emotional desensitization of the subject to the presence of the observer and to the procedure of sphygmomanometry.

Observations on the relative importance of these procedures have been made as follows. Patients were fasted overnight for between 10 to 12 hours and, next morning, were transferred in their beds to a quiet, warm room where they rested for a period of half an hour. At the end of this time the observer entered, adjusted the sphygmomanometer, and measured the blood pressure. This pressure is the basal blood pressure as defined by the above-mentioned societies. The measurements of the blood pressure were then continued without intermission for a further period of half an hour in order to secure whatever additional fall of blood pressure could be obtained by the method of emotional desensitization already described.

Results and Discussion

The Relationship between the Levels of the Casual, Basal, and Supplemental Blood Pressures in Healthy Males

The casual, basal, and supplemental blood pressures were measured in a number of healthy young males of European extraction and also in Egyptian males, using the method described by Alam and Smirk (1943, a). The relationship between the casual blood pressure and the supplemental pressure is set out in Fig. 1. It is seen that for the systolic pressure, higher

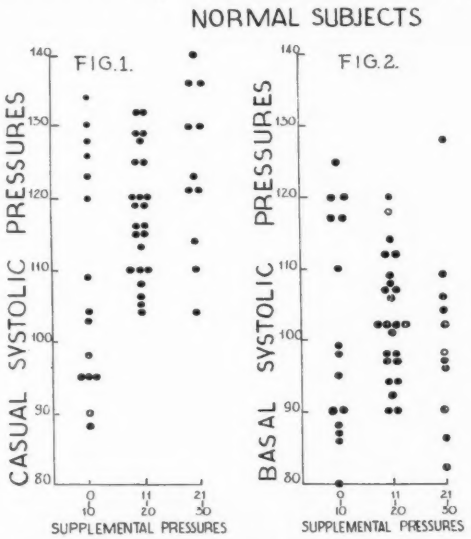


FIG. 1.—The ordinate gives the casual systolic pressure in millimetres of mercury for each of the 50 normal subjects. The subjects are arranged in three groups according to the magnitude of their supplemental (casual *minus* basal) pressures, viz. 0–10, 11–20, 21–30 millimetres of mercury. It is seen that subjects with a high supplemental systolic pressure have a better expectation of having a high casual systolic pressure.

FIG. 2.—The ordinate gives the basal systolic pressure in millimetres of mercury for the 50 normal subjects represented in Fig. 1. The subjects are arranged in three groups according to the magnitude of their supplemental (casual *minus* basal) pressures, viz. 0–10, 11–20, 21–30 millimetres of mercury. It is seen that a high supplemental systolic pressure does *not* increase the expectation of the subject having a high basal systolic pressure.

casual readings occur among patients with higher supplemental systolic pressures and lower casual readings tend to occur among patients with lower supplemental pressures. The relationship of these casual and supplemental pressures has been worked out by statistical methods and is significant, the correlation coefficient being +0·48. A similar relationship was found to exist between the casual and the supplemental diastolic pressures, the correlation coefficient being +0·50.

In Fig. 2 is set out the relationship between the supplemental and the basal systolic pressures in this same series of subjects. It is evident from the figure that when we compare the basal pressures of subjects whose supplemental pressures are high with those whose supplemental pressures are low we find the distribution of the basal pressures are much the same in the two groups. Any difference between them is not statistically significant, the correlation coefficient being −0·07. A similar analysis has been made of the relationship between the basal and supplemental diastolic pressures and a similar absence of relationship is established, the correlation coefficient being −0·11.

The Relationship between the Levels of the Casual, Basal, and Supplemental Blood Pressures in Patients with Essential Hypertension

In Fig. 3 is set out the relationship between the supplemental and the casual systolic pressures in a group of patients with essential hypertension. Some of the patients are those whose pressures were set out in Fig. 4 of a previous paper (Alam and Smirk, 1943, b), and the remainder are new cases. The general trend of the results is the same for the two sets. It is seen that groups of patients with higher supplemental pressures have as an average higher casual blood pressures and vice versa. The relationship between the supplemental pressures and the basal pressures for the two series of individuals is summarized in Fig. 4 of the present paper. It is found that groups of patients with hypertension selected for their high supplemental pressures do not have appreciably higher basal pressures than do groups of patients with hypertension who are selected for their low supplemental pressures. The figures when analysed statistically show no significant correlation between the heights of the supplemental systolic and of the basal systolic pressures, the correlation coefficient being −0·06; nor between the supplemental diastolic and basal diastolic pressures, the correlation coefficient being −0·08.

Statistical Significance of these Results

Where C=casual blood pressure, B=basal blood pressure, and S=supplemental blood pressure: C=B+S.

Now it has been shown that within a uniform class of individuals, e.g. all normals or all patients with essential hypertension, the statistical expectation of an individual having a high or low value of B is not influenced by the value of S. That is to say, if from a group of individuals we select out those who have high values of B and those who have low values of B the average values of S will not differ significantly in the two groups; (shown experimentally above).

Therefore, as C=B+S, a group of patients selected for their higher range of basal pressures will be found to have a higher range of casual pressures. Likewise a group selected for their higher range of supplemental pressures will be found to have a higher range of casual pressures. A group selected for high values of the casual pressure will contain a preponderance of those in whom a high basal pressure happens to have coincided with a high supplemental pressure. A low casual pressure will occur when a low basal pressure coincides with a low supplemental pressure.

Now, if a random series of blood pressure readings are subdivided into groups, the first group containing the highest casual blood pressures, the second group the next highest, and so on down to the lowest group; then since C=B+S and B and S are independent variable

it follows that the highest values of B and of S are associated together in the first group and the lowest values associated in the lowest group. In the middle groups both B and S cover a wide range, but the average B and the average S are both of intermediate magnitude.

This way of arranging results inevitably brings about a juxtaposition of high basal with high supplemental pressures and of low basal with low supplemental pressures. The juxtaposition has been pre-determined by the ordering of results in descending order of magnitude

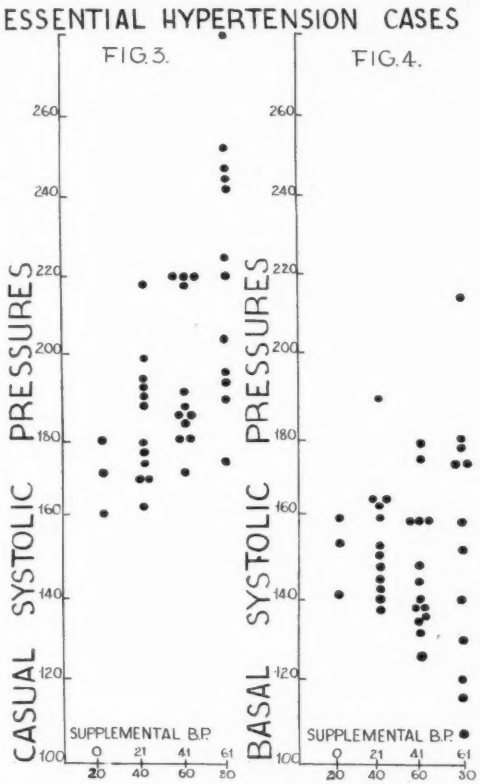


FIG. 3.—The ordinate gives the casual systolic pressures in millimetres of mercury for each of the 39 hypertensive subjects. The subjects are arranged in four groups according to the magnitude of their supplemental (casual *minus* basal) pressures, viz. 0–20, 21–40, 41–60, 61–80 millimetres of mercury. It is seen that subjects with a high supplemental systolic pressure are more likely to have a high casual systolic pressure.

FIG. 4.—The ordinate gives the basal systolic pressures in millimetres of mercury for the 39 hypertensive subjects represented in Fig. 3. The subjects are arranged in four groups according to the magnitude of their supplemental (casual *minus* basal) pressures, viz. 0–20, 21–40, 41–60, 61–80 millimetres of mercury. It is seen that a high supplemental systolic pressure does *not* increase the expectation of the subject having a high basal systolic pressure.

of the casual blood pressure and the juxtaposition has no biological significance whatsoever. This somewhat inconspicuous error in selection is apt to lead to rather fundamental differences in the conclusion drawn.

Let us consider the following purely numerical example. Take the following 12 values of B: 120 120, 130 130, 140 140, 150 150, 160 160, 170 170; now let the values of S be 20 for one and 60 for the other of these paired values of B. Thus, in our artificial example, the distribution of the values of S does not bear any relation to the value of B 20 60, 20 60, 20 60, 20 60, 20 60, 20 60, the values of C being equal to B+S are as follows: 140 180, 150 190, 160 200,1 70 210, 180 220, 190 230. Arrange these results in order of magnitude of C:

C	B	S	C	B	S	C	B	S
230	170	60	190	170	20	170	150	20
220	160	60	190	130	60	160	140	20
210	150	60	180	160	20	150	130	20
200	140	60	180	120	60	140	120	20

Average the 4 highest, 4 middle, and 4 lowest values of the table and we obtain:

	C	B	S
High group	215	155	60
Middle group ..	185	145	40
Low group	155	135	20

Thus we have a series of averages in which casual, basal, and supplemental pressures show parallel variations.

It is very tempting from such an analysis to draw the conclusion which was drawn by the editor of the *British Heart Journal*, from a similar analysis which he made, in commenting upon a previous publication of Alam and Smirk, namely, that there is a relationship between the levels of the basal and supplemental pressures. This relationship, however, does not exist, the figures in the numerical example being so chosen that there should be no such relationship. It follows, therefore, that this statistical method as used by the editor is inapplicable. The parallel increase in the values of basal and supplemental pressures in the above table and in that published by the editor in his comment are the result of using a method of selection which pre-determined the final result.*

Mr. Williams, statistician to the economics department of the Otago University, has been kind enough to work out for me the correlation coefficients of various relationships.

TABLE I

VALUES OF CORRELATION COEFFICIENTS

	No. of cases	Correlation coefficients			Squares of coefficients	
		Rbc	Rcs	Rbs	R^2bc	R^2cs
Normal systolic	50	0·84	0·48	−0·07	0·71	0·23
Normal diastolic	54	0·77	0·50	−0·11	0·59	0·25
Hypertensive systolic	39	0·75	0·61	−0·06	0·56	0·37
Hypertensive diastolic ..	37	0·75	0·59	−0·08	0·56	0·35

In the above table Rbc represents the relationship between basal and casual pressures, Rcs the relationship between casual and supplemental pressures, and Rbs the relationship between basal and supplemental pressures.

With normal pressures, systolic and diastolic, and hypertensive pressures, systolic and diastolic, the expectation is that individuals with the higher basal pressures are more likely to have high casual pressures and vice versa. The chance of the blood pressure figures, upon which these relationships are based, occurring by coincidence are less than 1/100,000 for each of the above four groups and taking all four sets together the chances of the relationship being coincidental must be less than one in ten million. There is also a direct correlation between the height of the supplemental pressures and the expectation of high casual pressures in all four groups. The chance of this happening by coincidence in the normal groups is less than 1/50,000 for each group and for the hypertensive groups is less than 1/100,000. Taking the four groups together the chance of coincidence is quite negligible.

Within the four groups studied, however, basal and supplemental pressures are independent

* " I am glad to publish this paper especially because it appeared to me that Fig. 4 of the paper by Alam and Smirk (1943, b) did not convincingly show that the basal and the supplemental pressures were independent variables. The further statistical analysis submitted in this present paper, however, seems conclusive evidence that this is so."—EDITOR.

variables. That is to say, in none of the four groups does possession of a high or low supplemental pressure increase or diminish appreciably the expectation of a high basal pressure. While the view is expressed that the basal blood pressure is an independent variable when we compare the different members of a *group* of individuals, yet this statement is in no way inconsistent with the view expressed earlier that, in the absence of any marked physiological change, the basal blood pressure of an *individual* is relatively constant for that individual.

The squares of the correlation coefficients for the relationship of casual to supplemental pressure are appreciably higher for the hypertensive groups (systolic and diastolic) than for the normal group (systolic and diastolic). This indicates that the supplemental pressure forms a significantly higher proportion of the casual pressure among the hypertensive than among the normal group.

Improvements in the Method of Measuring the Basal Blood Pressure

A comparison has been made in a series of 13 subjects of the level of the basal blood pressure. (1) Determined by the method recommended by the committees of British and American cardiologists; in essence this consists of preparation of the patient in the manner laid down for basal metabolic rates prior to the measurement of the blood pressure. (2) Immediately after this measurement the procedure of emotional desensitization recommended by Alam and Smirk, 1943, a, was applied with the object of determining whether this additional procedure caused a further decrease in the level of the blood pressure. (3) The patient then had breakfast, assumed normal ward life, and later on in the day returned for the measurement of the basal blood pressure by the procedure recommended by Alam and Smirk. That is to say the procedure of emotional desensitization was carried out without having the patient in the basal metabolic state.

The results are set out in Table I. It will be seen that rest and emotional desensitization produce blood pressures which are similar to those obtained by the procedure recommended by the committees of British and American cardiologists. The combination of the two procedures, however, appears to give still lower values for the basal blood pressure than the use of either separately. It seems improbable that much lower values of the basal blood pressure will be obtained by other procedures, but it is not unlikely that minor improvements can be effected.

TABLE II

COMPARISON OF METHODS OF MEASURING BASAL BLOOD PRESSURE

Subject	Casual blood pressure	Basal blood pressure by three methods		
		Method of cardiological committees	Method of emotional desensitization	Combination of two methods
D	192/118	188/100	182/124	164/98
C	122/86	122/86	110/79	106/68
J	118/54	96/58	106/52	92/54
McN	98/66	106/64	94/75	96/60
Mu	130/74	132/76	110/77	122/74
Mo	104/74	98/62	94/64	80/62
S	134/90	130/90	112/80	128/88
Wi	122/66	128/68	118/55	124/66
Ma	114/78	106/78	110/76	92/78
N	120/60	106/70	110/58	94/61
O	122/68	112/68	116/58	110/65
W	130/76	114/74	116/68	112/70
Me	116/72	92/60	106/68	90/65
Average ..	124·8/75·5	117·7/73·4	114·2/71·8	108·5/69·9

Summary

The casual blood pressure may be regarded as the sum of the basal blood pressure and th supplemental pressure; this last represents the degree of blood pressure elevation above th basal level due to whatever degree of physical, emotional, and supra-basal metabolic activit is present at the time of blood pressure measurement. The basal pressure is the pressur measured at a time when physical, emotional, and metabolic activity are reduced to a physio logical minimum. In cases where it is impossible to do this because of restlessness or emotiona tension, the reading obtained should not be described as basal. Failure to obtain the tru basal reading will not always be apparent to the observer especially when, as is most commonl the case, the failure is due to emotional reasons.

Both normal and hypertensive subjects with a high basal pressure have a greater statistica expectation of having a high casual pressure than do those whose basal pressure is low. Like wise those with high supplemental pressures have a greater statistical expectation of a high casual pressure than do those whose supplemental pressure is low.

In comparing one individual with another the basal and supplemental pressures on the other hand are independent variables in the sense that the level of the basal blood pressure in an individual is no guide to the probable level of the supplemental pressure.

Most statistics concerning the level of the blood pressure are concerned with the casual readings. The fact that when comparing one individual with another, within a comparable physiological group, the casual blood pressure is to be regarded as the sum of two independent variables has statistical implications which are discussed.

The supplemental pressure forms a significantly higher proportion of the casual pressure among patients with essential hypertension than among normal subjects.

An improved method is recommended for determining the basal blood pressure.

I wish to express my thanks to Miss Fulton for technical assistance.

References

Alam, M., and Smirk, F. H. (1943, a). *Brit. Heart J.*, **5**, 152.
—— (1943, b). *Ibid.*, **5**, 156.
Kilpatrick, J. A. Personal communication.

MYOCARDIAL INFARCTION

BY

T. E. LOWE AND W. B. WARTMAN

From the Department of Pathology, University of Melbourne, and the Institute of Pathology, Western Reserve University and University, Hospitals of Cleveland, Cleveland, Ohio

Owing to postal delays caused by the authors' movements, this summary of their recent paper (*British Heart J.*, **6**, 115–128, 1944) *was not received in time to print with the paper. The opportunity is taken of adding one sentence and correcting two misprints.*—EDITOR.

Any discussion of myocardial infarction should correlate the pathological changes with the anatomical structure of the heart. In this paper a review of the anatomy of the cardiac muscles and of the coronary arterial tree and the diseases thereof that may lead to muscle infarction is given. The consequences of interference with the blood flow in this tree are discussed.

The ventricular and auricular (atrial) walls are composed of several muscles, which are in reality as distinct as the three glutei muscles making up the gluteal mass. The separation of these muscles was first shown by anatomical dissection, and has been confirmed by the demonstration of independent blood supplies, and their individual involvement in various pathological states.

Anastomotic channels of arterial size between major coronary arteries exist of all ages. Pressure difference between the ends of any vessel is the factor which determines the direction of blood flow in that vessel. In a normal coronary circulation arterial anastomoses will have approximately the same pressure at either end, so that the blood supply will be small and may easily change in direction from time to time. In hearts the seat of obstructive arterial changes, marked difference of pressure between the ends of the anastomotic channels may easily occur, and then these vessels enlarge and become visible to the naked eye. The distribution of fields of supply will also become upset and it will then be impossible to predict the field of supply of any one of the major coronary arteries.

No one arterial branch supplies the whole of any one ventricular muscle. It is important that the parent artery, which gives branches to the pericardial portion of a superficial muscle, gives branches also to the endocardial portion of that muscle, but not to the deep branches in between.

No essential difference exists between diseases of the arteries of the heart and those of other organs of the body. Regardless of which portion of the coronary tree is affected, the gravity of the lesion is largely determined by the degree of vascular obstruction. In most cases thrombosis is secondary to underlying vascular disease, and primary thrombosis of the coronary arteries has not been encountered. A discussion of the various diseases of the coronary arteries follows. The importance of arteriosclerotic intimal hæmorrhage in precipitating thrombosis and vascular occlusion is stressed. Similar hæmorrhages in the media lead to dissecting aneurysm.

Myocardial ischæmia is discussed under the following headings: (1) infarction of the ventricular wall; (2) interference with ventricular function; (3) rupture of the ventricle; (4) ventricular aneurysms; (5) infarction of the atrial wall; and (6) electrocardiographic changes. The effects of sudden and gradual occlusion in normal and diseased coronary

arteries are considered. The resulting infarcts may involve parts of several muscles (whole thickness of ventricular wall), or may be confined to a portion of one muscle, or may form scattered small foci.

Interference with ventricular function may result either from an inability of the ischæmic heart adequately to expel blood or from the development of abnormal rhythms.

The physical basis of aneurysm formation is the same in both ventricle and aorta, for in both places muscle tissue is active in withstanding pressure, and when enough of it is destroyed and replaced by collagen, gradual stretching and sac formation occurs. Two types of ventricular aneurysms are described. Basal aneurysms show two laminar scars indicating that destruction of two deep muscles is essential to their formation. Apical aneurysms, in contrast, show a single laminar scar due to the involvement of the superficial musculature.

The principles outlined in discussing ventricular infarcts are strictly applicable to those occurring in the walls of the auricles. Auricular infarcts occur in about 17 per cent of cases of ventricular infarction and usually involve the right auricular appendage. Disturbance in auricular electrical activity in such cases may suggest damage of the auricular muscles, possibly due to infarction.

The paper concludes with a brief discussion of the limitations of electrocardiographic changes.

ERRATA

Page 119.

Line 6. *Insert* " In most cases thrombosis is secondary to underlying vascular disease, and hence may complicate any of the lesions described below. We have not encountered primary thrombosis of the coronary arteries."

Line 16. *Insert* " by " between " muscle " and " fibrous tissue."

Line 19. *Insert* " 20 " for " 10 " before per cent.

Corrected References

Flett, R. L. (1927). *J. Anat.*, **62,** 439.
Wartman, W. B. (1933). *Amer. J. med. Sci.*, **197,** 7.
—— (1940). *American Association for the Advancement of Science*, Publication 13.

A CASE OF TUBERCULOUS PERICARDITIS

BY

A. M. BARRETT AND LESLIE COLE

From the Department of Pathology, University of Cambridge, and Addenbrooke's Hospital

Received October 21, 1944

Uncomplicated tuberculous pericarditis is not common, and this case is described because it gives a good picture of the march of the disease both clinically and pathologically.

Description of Case

A man, aged 22, who worked as a shop assistant, was admitted to Addenbrooke's Hospital on March 11, 1943, with the following history. About mid-February he first began to feel generally out of sorts and over the space of a few days developed a dry, irritating cough which kept him awake at night, a dull pain over the præcordium, nausea, weakness, and slight breathlessness on exertion. These symptoms persisted until his admission.

His previous health had been good and the only illness he remembered was an attack of " pleurodynia " at the age of 18. His family history was healthy with no tuberculosis.

On admission the heart was greatly enlarged both to left and right, the apex beat could not be seen or felt, the sounds were faint and tic-tac in quality, the pulse small, regular, and rapid (110), the respiratory rate 22, the temperature intermittent and rising to 100 or 101, and the blood pressure 110/80.

The most arresting physical sign was a loud rub audible over the whole pericardium but most marked at the base.

The cardiogram showed low voltage curves with inversion of T in leads I, II, IVR, and IVF (Fig. 1) and X-ray showed the typical shadow of a large pericardial effusion (m.t.d. 17 cm.; see Fig. 2). The sedimentation rate (Westergren) was 60 mm. in one hour.

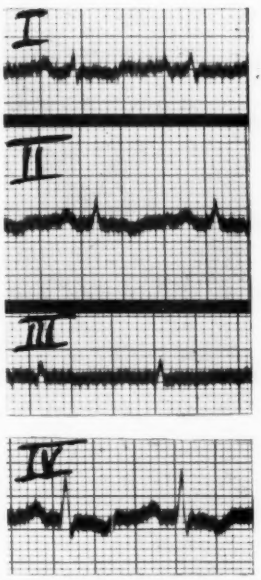


Fig. 1.—Cardiogram (25/4/43) showing P–R 0·16 sec. and inversion of T waves.

Progress. Except for a period of two months in September and October when he rested at home, he remained under observation in hospital until his death on December 9.

The progress of the disease appeared to fall into three clinical phases.

(1) The phase of increasing effusion leading to congestive failure (4 months).

(2) The phase of decreasing effusion with temporary recovery (3 months).

(3) The phase of increasing thickening and fibrosis of the pericardium and congestive failure ending in death (3 months).

Phase 1. During this phase the rub disappeared, there was a progressive increase in the size of the effusion and the temperature fell gradually to normal in six weeks. In the first few weeks the blood pressure fell to an average of 90/65 at which level it remained for about three months and the veins of the neck became distended and remained so. This phase culminated in an attack of congestive failure with a large pleural effusion at the right base, some ascites and slight general œdema.

Phase 2. Following recovery from the congestive failure (Fig. 3) the pericardial effusion began to subside gradually and there was marked general improvement with a steady rise of blood pressure to an average level of 110/80 and lessening venous distension. By the end of July his resting pulse rate was 80–100, and he appeared to

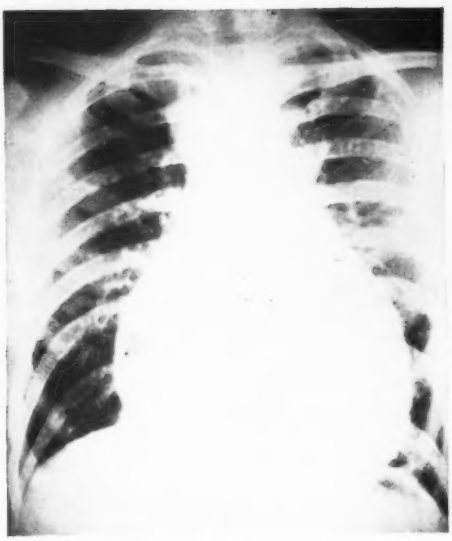


FIG. 2.—Radiogram of the heart (2/4/43) showing rounded dilatation of the pericardial sac.

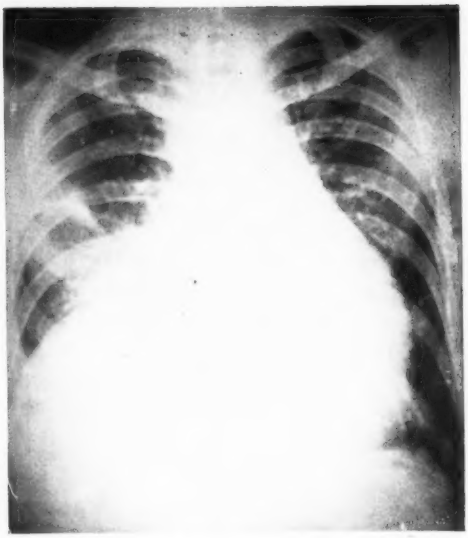


FIG. 3.—Radiogram of the heart (8/7/43) after recovery from an attack of congestive failure with right basal effusion.

have recovered some measure of compensation. His sedimentation was then 12 mm. His condition then appeared to remain stationary and had not changed when he was readmitted for further observation in October.

Phase 3. The diminution in size of the area of cardiac dullness with increasing irregularity of outline by X-rays suggested progressive thickening of the pericardium (Fig. 4). In November, steady deterioration began. The pulse rate gradually rose from an average of 80, the blood pressure steadily fell from an average of 110/85, the pulse pressure also fell, and the venous congestion again became more marked and pulsus paradoxus very pronounced. Congestive failure with gross œdema

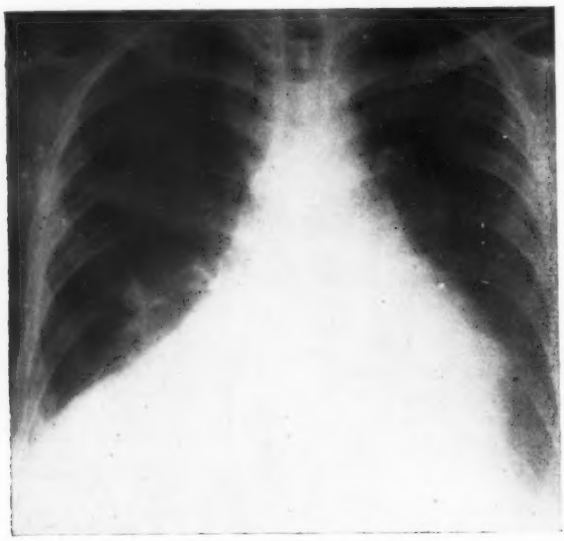


FIG. 4.—Radiogram of the heart (27/10/43) showing the pericardial sac diminished in size and irregular in outline.

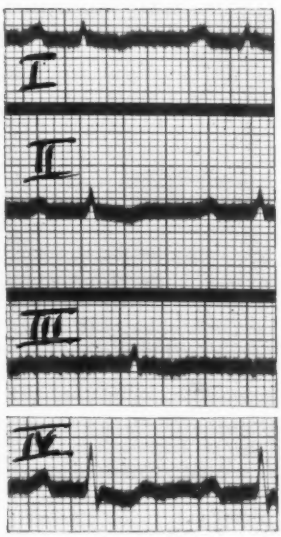


FIG. 5.—Cardiogram (28/10/43), latent heart block with P–R 0·24 sec.

gradually supervened and he died on December 9. During the last two months the sedimentation rate was below 6 mm. The cardiogram at the end of October showed still lower voltage curves with T III also inverted and the P–R interval, which had been previously normal, prolonged to 0·24 sec. (Fig. 5).

The *leucocyte count* (27/5/43) was 9,800 cells per c.mm. The *differential count* was normal.

Pericardial fluid. This was yellowish and slightly opalescent with a fine feathery clot. A few small lymphocytes and some fibrin were present but no red cells. Cultures were sterile. A guinea-pig inoculated on April 28 appeared to remain well until October but died on October 8. The cause of death was very extensive, rather hyperplastic tubercle involving glands, liver, spleen, and lungs. Tubercle bacilli were found in stained films. A *Mantoux test* (1/11/43; human, 1 : 10,000) was positive.

Treatment. 300 c.c. of fluid were aspirated slowly from the pericardium on April 27. This did not appear to have any beneficial effect on either the general or local condition, nor did it cause any change immediate or remote on the very low blood pressure. The general condition was worse during the succeeding few days, and for this reason it was not repeated. Suzman (1943) noted the absence of any effect on the blood pressure in a similar case.

During the first attack of congestive failure, ammonium chloride, 30 grains, followed by mersalyl, 1 c.c. and later 2 c.c. intramuscularly, were given with only moderate response. The fourth injection was followed in three minutes by severe collapse in which the patient nearly died, after which its use was abandoned. Digoxin was given at various times, but only appeared to have a beneficial effect during the first attack of congestive failure. Aspiration of the pleural effusion caused marked and sustained improvement.

Clinical Comment

The diagnosis of tuberculous pericarditis was made in the early stages on the clinical findings, but was only confirmed by guinea-pig inoculation; it is noteworthy that the guinea-pig appeared to maintain health for five months after the inoculation, an unusually long period. Constitutional symptoms in the patient were notably slight throughout the illness. The temperature settled during the first six weeks and did not rise again, the appetite remained fairly good, and there was no abnormal sweating. After the first few weeks the sedimentation rate was never higher than 12 mm. in one hour. Apart from the two attacks of congestive failure, symptoms were very slight. During the second phase there was considerable improvement with a rise of blood pressure and diminution of venous congestion, and for about three months there did not appear to be any deterioration. Reviewing the whole course of the disease, it seems probable that this apparent improvement was illusory and occurred because the relief afforded by the absorption of excessive pericardial fluid had not yet been offset by the gradual thickening of the visceral pericardium with its progressive hampering effect on the action of the heart. As this process became more advanced, terminal failure gradually set in.

Post-mortem Examination

A deeply cyanosed well-developed young man with œdema and engorgement of veins in neck and elsewhere. Great excess (740 c.c.) of cloudy greenish-lemon fluid in much enlarged pericardial sac, which has a thick deposit of gelatinous yellowish fibrin on its inner surface, particularly over the right auricle and on the adjacent parietal pericardium (Fig. 6). Pericardium everywhere greatly thickened (0·2–0·3 cm. thick) and tough, grey to pinkish-grey in colour where it is neither covered by fibrinous exudate nor beset with greyish-white granulomatous plaques of which there are many. No adhesions between parietal and visceral pericardium except slightly at base. No constriction, not even of slight degree, of superior or inferior venæ cavæ nor of the main pulmonary vessels. Rather small heart, its ventricles almost empty and its auricles containing less than 50 c.c. blood and clot in all. Myocardium brown or brownish-red and apparently normal (right ventricle 0·6–0·7 cm. thick, left ventricle 1·5 cm. thick). Heart valves normal. Conspicuous hypertrophy of the wall of the inferior vena cava, which immediately below the liver appears about twice as thick as normal and is sufficiently rigid to prevent the collapse of the vessel after it has been opened. Only slight

FIG. 6.—Photograph of the heart showing a thickened and distended pericardium beset with granulomatous plaques.

atheroma of aorta, its abdominal part being rather narrower than the average but within normal limits. No excessive atheroma of pulmonary arteries. Non-specific inflammatory changes only in several moderately enlarged lymph glands on the outer surface of the pericardium near the hilum of the left lung. Ill-defined firm greyish areas suggesting granulomatous tuberculosis in several lymph glands on the left posterior aspect of the pericardium. Caseous tuberculosis of one small mediastinal lymph gland near the left bronchus, between the main left pulmonary artery and the arch of the aorta; this gland was about 1·5 cm. from the pericardium at its nearest point, and its soft crumbling centre surrounded by a dense zone of fibrosis. Small (0·2 cm. diam.) calcareous nodule surrounded by fibrous tissue in upper lobe of left lung near apex. Both lungs partially collapsed by pleural effusions and slightly congested. Clear yellowish fluid in serous cavities: right pleura 1870 c.c., left pleura 920 c.c., peritoneum 2640 c.c. Mesenteric lymph glands rather large but normal in appearance. Changes in the other organs were those of chronic venous congestion. Heart not weighed because preserved with pericardium for mounting.

Microscopic. Heart. Chronic tuberculous pericarditis with much increase of fibrous tissue. No definite lesions in myocardium. *Lymph glands (from posterior surface of peri-*

cardium). Typical granulomatous tuberculosis with abundant giant cells but no caseation. *Inferior vena cava.* Conspicuous thickening of wall. *Mesenteric lymph gland.* Very wide but almost empty sinuses and atrophy of lymphoid tissue; no tuberculosis.

The changes in the other organs were those of chronic venous congestion.

Bacteriological. By guinea-pig inoculation with pericardial fluid tubercle bacilli of eugonic human type were demonstrated.

The Mechanism of Impairment of Cardiac Function

During the necropsy a somewhat crude attempt was made to determine whether the pericardial effusion itself at the time of death was likely to have caused any serious impairment of cardiac function.

Presumably such impairment would be mainly due to limitation of the intake of blood into the auricles during diastole. If V(e)=the volume of the effusion, V(b)=the total volume of blood that enters and is expelled from the heart at each beat, and V(h)=the volume of the substance of the heart itself, then impairment of cardiac function due to an effusion will not be expected unless V(e)+V(b)+V(h) is sufficiently great to stretch the parietal pericardium so that before the end of diastole the pressure inside the pericardium (and hence in the auricles) becomes equal to that in the venæ cavæ. V(b) will then be reduced and the function of the heart impaired. We attempted at necropsy to discover whether this critical volume had been attained by measuring the relationship between known increases in the total volume of the pericardial contents and the intra-pericardial pressure.

When the thorax and abdomen had been opened, and before any further dissection, the superior and inferior venæ cavæ were ligatured immediately above and below the intact pericardium. This was done in order to prevent alterations in the volume of the pericardial contents due to blood being squeezed out of the heart during the subsequent manipulations. A glass funnel was attached to one end of a length of rubber tubing and a blood transfusion " taking " needle to the other end. The needle was then inserted into the pericardium (through the diaphragm, to minimize leakage) and 35 c.c. pericardial fluid was allowed to escape through the tube into a bottle. This sample was reserved for examination, but the original volume of the effusion was restored by pouring 35 c.c. water back through the funnel into the pericardial sac. The funnel was now held in such a position that a mark on its stem was 10 cm. above the pericardium and water was poured in until the level remained stationary at the mark. The volume of water that had been added was noted, and the funnel was then raised until the mark was 20 cm. above the pericardium. The process was then repeated; and similarly with the level at 30 cm., and 50 cm. The same measurements were made on another subject whose heart and pericardium appeared normal. The results were as follows:

Intra-pericardial pressure (cm. water)	Volume of fluid introduced into pericardium (c.c.)	
	Patient	Control
10	140	260
20	180	285
30	215	305
40	235	312
50	260	330

Strictly, in comparing these measurements, allowance should be made for the volume of blood and clot present in the chambers of each heart, but it was not found possible to measure this volume accurately without spoiling the heart as a museum specimen, and this we were loath to do. However, the volume of the contents was relatively small (less than 50 c.c.) in each of the hearts and there was no great inequality in the amounts.

These results suggest that an effective venous pressure of 10 cm. water should have enabled the heart to deal with at least 140 c.c. blood at each beat if its action were hampered only by the mechanical effects of the effusion. The average systolic output of normal adults at rest

is between 60 and 70 c.c. (Grollman, 1932), but this figure is the output of one ventricle only: the total output of the heart is 120–140 c.c. per beat. Thus it seems that in spite of the effusion the patient should have been able to maintain a normal cardiac output while resting, provided that his effective venous pressure was not less than 10 cm. water. His actual venous pressure was not measured, but the conspicuous venous engorgement observed during life and the thickening of the wall of the inferior vena cava seen at necropsy suggest that the pressure was probably greater than this, and hence that the impairment of cardiac function about the time of death was not due to the mechanical effects of the effusion.

Of other possible causes of impairment of cardiac function, the greatly increased thickness and rigidity of the visceral pericardium appears the most likely. There was little histological evidence of myocardial damage although this had been indicated by the prolonged P–R interval of the cardiogram. Constriction of the vessels entering the heart was excluded.

Summary

This patient's initial tuberculous infection was situated near the apex of the left lung and was very small. The infection apparently spread from the lung to a mediastinal lymph gland between the left bronchus and the pericardium, and from this gland to the pericardium—though no definite track of infection between the gland and the pericardium was in fact found at necropsy. Tuberculous pericarditis with effusion followed, and death was due to congestive heart failure. There was no evidence of tuberculosis elsewhere in the body. Evidence is given which suggests that at the time of death the pericardial effusion played a relatively small part in limiting cardiac efficiency, and it is suggested that increased thickness of the visceral pericardium with loss of its pliability was the chief cause.

We wish to thank Dr. J. F. Gaskell for permission to investigate and publish this case, Dr. C. H. Whittle for some of the pathological investigations, and Dr. Ff. Roberts for the X-ray examinations.

References

Grollman, A. (1932). *The Cardiac Output of Man in Health and Disease*, London.
Suzman, S. *Brit. Heart J.*, **5**, 19.

PERFORATION OF THE INTERVENTRICULAR SEPTUM DUE TO CARDIAC INFARCTION

BY

ANNE M. WOOD

From the Harrogate General Hospital

Received August 10, 1944

Until December 1943 thirty-eight cases of rupture of the interventricular septum have been reported; of these eight were diagnosed ante-mortem. Rupture of the septum usually occurs in the seventh and eighth decades in patients who have had long-standing high blood pressure. It is more common in first infarctions, where the infarct is small and the blood pressure remains above 160/100 after infarction. The average time of rupture is between the third and twelfth days (Edmunson and Hoxie, 1942).

Stanley (1937) reported that, at the time of rupture of the septum, his patient complained of sudden substernal pain and became shocked. After rupture a systolic murmur, which may be rough or blowing, has been noticed over the sternum in the fourth and fifth interspaces in all reported cases, generally accompanied by a systolic thrill (Sagar, 1934). In all cases observed within two or three hours of rupture there has been cyanosis and dyspnœa and usually there has been some degree of congestive failure throughout the illness; death usually being due to right ventricle failure (Bayley and Fader, 1941).

Although most reported cases have died during the first week after perforation of the septum, diminution of the congestive failure has followed prolonged use of mercurial diuretics (Wood and Livezey, 1942) and digitalis therapy (Leonard and Daniels, 1938).

Seven cases have been reported that lived for more than four weeks, of which Moulton (1942) mentions four. The longest recorded duration of life after perforation is four years and ten months (Wood and Livezey, 1942). Gross and Schwartz (1936) record a case which survived two months and Stanley (1937) one which lived five months.

Case Report

E. M. V., a woman aged 69 years, was admitted to hospital on 27/10/43. She had been known to have high blood pressure for the preceding year. For fourteen months before admission she had complained of aching across the shoulders and down both arms, occurring on exertion and immediately relieved by rest. On 17/10/43, ten days before admission, she had an acute attack of pain in the shoulders and down both arms, which came on at rest. The pain lasted about an hour, and was followed by a feeling of faintness. After the attack she became increasingly dyspnœic on exertion, but there was no recurrence of the pain.

On admission to hospital she was not cyanosed and there was no dyspnœa at rest. The pulse was regular at a rate of 120. The blood pressure was 100/70. The apex beat was four and a half inches to the left in the fifth interspace and was diffuse and moderately heaving. A thrill was not felt. A blowing systolic murmur was heard over the lower sternum, replacing both sounds in this area; it was conducted towards the axilla and up the sternum. There was slight œdema over the sacrum. The veins of the neck were not distended and the liver was not palpable. Crepitations were heard at both pulmonary bases.

A cardiogram (Fig. 1) showed evidence of recent posterior infarction. A radiogram showed cardiac enlargement to the right and left, and basal pulmonary congestion. The white count was 15,000, of which 68 per cent were polymorphonuclear. The blood urea was 55 mg. per 100 c.c. of blood. Urine analysis showed a trace of albumin, an occasional erythrocyte, and a few leucocytes. The blood sedimentation rate was 14 (Wintrobe).

She was treated with ammon. chlor., grains 30, and with neptal, 2 c.c. intramuscularly every third day, which produced a moderate diuresis, and later with cardophylin intravenously and by mouth, to which she showed no response.

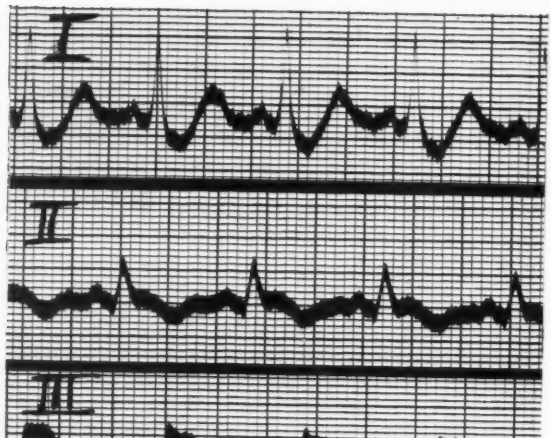


FIG. 1.—Electrocardiogram with evidence of posterior infarction—depression of the S–T junction in lead I, and bowed inversion of T in leads II and III.

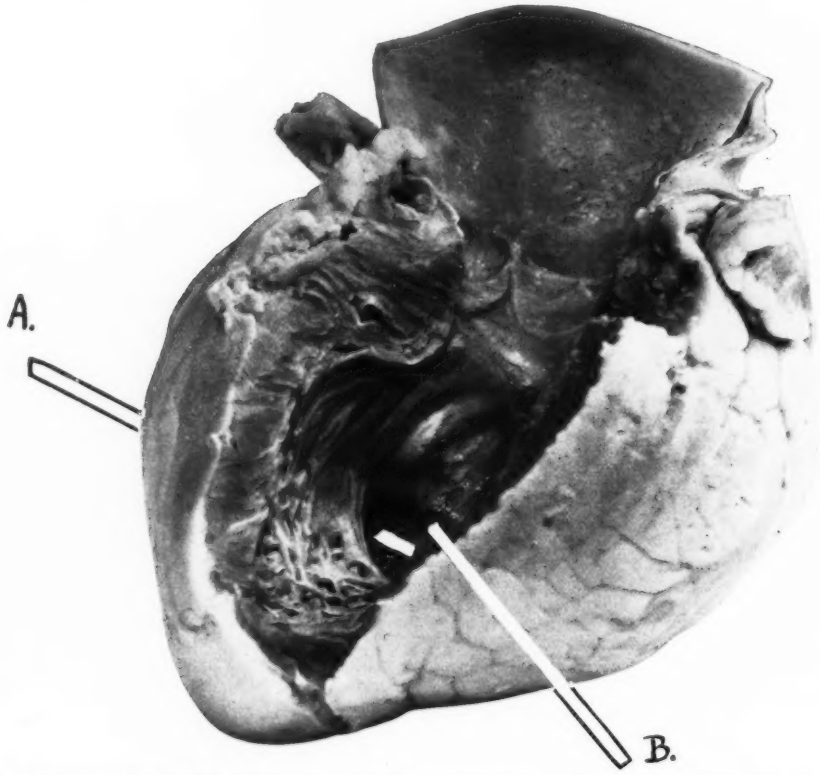


FIG. 2.—Photograph of heart showing perforation of interventricular septum. (A) Perforation in the interventricular septum. (B) Aneurysmal dilatation seen from the left ventricle.

The heart sounds remained constant and there was no noticeable increase in the heart size. A cardiogram taken after four weeks continued to show signs of infarction but no other abnormality. The pulse rate was persistently rather rapid, varying between 88 and 124. Crepitations persisted at the pulmonary bases throughout her illness but the sacral œdema rapidly disappeared. There was no further development of congestive failure, though the patient frequently complained of nausea and vomited occasionally.

The patient lived for five weeks after admission to hospital, during which time her general condition improved slowly until two hours before death, when she complained of gradually increasing præcordial pain with nausea and faintness. She became collapsed and her blood pressure fell. This was considered to be due to further cardiac infarction.

Post-mortem findings. (Dr. S. Wray). The heart weighed approximately 400 g. and showed slight general enlargement. The thickness of the left ventricle was 18 mm. (normal 6–12 mm.), and of the right, 9 mm. (normal 3·2 mm.).

The lumen of the right coronary artery was almost obliterated by old thrombus but was just patent. The posterior part of the left ventricle and the posterior part of the interventricular septum showed ischæmic changes due to an infarction of some weeks duration. In the posterior part of the septum, including the membranous septum, there was an aneurysmal dilatation extending into the right ventricle. The base was 30 x 20 mm. in area, and it was 15 mm. deep. At its apex there was a slit-like perforation, 10 mm. long, giving free communication between the ventricles. The walls of the aneurysmal sac, and of the perforation, at its apex, were smooth, suggesting that the lesion was of some weeks duration. There was nothing to suggest that the lesion was of congenital origin. (Fig. 2). The part of the endocardium of the right ventricle immediately opposite the perforation showed a thickened area, whiter than the surrounding tissue.

The descending branch of the left coronary artery was completely occluded in its upper part by an atheromatous plaque and super-added recent thrombosis. The myocardium of the anterior part of the left ventricle showed very recent infarction.

The valves of the heart were normal. The right pleural cavity contained about half a pint of clear yellow fluid. The lungs showed basal œdema only. The liver was normal in size, but of mild nutmeg appearance.

Discussion

Before death the diagnosis made with some confidence was a rupture of the interventricular septum following posterior cardiac infarction. The diagnosis was based on the recent development of a systolic murmur beneath the sternum, following a single cardiac infarction, in a patient who was known to have had high blood pressure.

The signs were not typical of the condition as it has been previously described, as there was no history of any initial shock, no systolic thrill, and the systolic murmur was blowing rather than rough. These atypical findings may be due to the fact that the infarcted septal area was first stretched to form an aneurysmal dilatation, and only later became sufficiently thin to perforate. In this case the perforation might occur slowly, so that there would be no initial shock. The absence of thrill might be due to a slow rate of blood flow through the perforation because of the presence of the aneurysm. Compensation for the abnormal circulation was established by the relative hypertrophy of the right ventricle. This explains the absence of marked congestive failure.

The effects of perforation of the interventricular septum in this case were a rapid pulse rate and persistent basal pulmonary œdema.

Summary

A case of rupture of the interventricular septum, accompanied by an aneurysmal dilatation of the septum is described. The signs were not typical. An explanation of the atypical findings is attempted.

I wish to thank Dr. C. W. Curtis Bain for his interest and help.

References

Bayley, R. H. and Fader, D. E. (1941). *Amer. Heart J.*, **21,** 238.
Edmunson, H. N. and Hoxie, H. J. (1942). *Ibid.*, **24,** 719.
Gross, H. and Schwartz, S. P. (1936). *Ibid.*, **11,** 626.
Moulten, S. E. (1942). *Arch. intern. Med.*, **69,** 108.
Sager, R. V. (1934). *Ibid.*, **53,** 140.
Stanley, D. F. (1937). *Amer. Heart J.*, **14,** 420.
Wood, F. C. and Livezey, M. M. (1942). *Ibid.*, **24,** 807.

CARDIO-AORTIC FISTULA

BY

ALASTAIR MACLEOD

From the London Hospital

Received September 12, 1944

A diastolic murmur heard along the right border of the sternum is regarded as evidence of aortic incompetence, but to this general rule of auscultation there is one exception, and this was present in the case reported here.

A labourer, aged 54, was admitted to the London Hospital with breathlessness and swelling of the legs. He had been quite well until two weeks before admission, when he complained of abdominal pain, vomiting, and great breathlessness. He attributed all his symptoms to indigestion. The pain and vomiting ceased after an hour, but breathlessness recurred on slight exertion. Occasionally effort induced a heavy retrosternal pain which radiated down the right arm. One week before admission he noticed swelling of his ankles. He had a slight cough but there was no sputum. His sleep had been disturbed by attacks of breathlessness. He had never had rheumatic fever nor syphilis; and he had been accustomed to heavy manual work all his life.

On admission he was orthopnœic, but cheerful and cooperative. He was pale and anæmic (hæmoglobin, 56 per cent). The pulse was irregular from auricular fibrillation and rapid (132 a minute). The blood pressure was 115/70. There was venous engorgement in the neck and prominent venous and arterial pulsation. A systolic thrill was felt over the carotid arteries. The apex beat was displaced as far as the anterior axillary line in the sixth intercostal space. The first and second heart sounds were heard over the apex and a third heart sound had been added. A harsh systolic murmur was audible all over the heart, but it was loudest in the aortic area: when the heart rate was slowed to 90 a systolic thrill was felt in the aortic area and a soft diastolic murmur became distinct at the right border of the sternum. This murmur was conducted towards the apex. At the same time the pulse became collapsing in character. There were many crepitations at the lung bases; the liver was distended and ascites was present; and there was pitting œdema of the legs up to the knees. The urine contained a cloud of albumin and the blood urea was 98 mg. per 100 c.c. The electrocardiogram showed auricular fibrillation, normal axis deviation, and inversion of the T waves in leads I and II. The patient was too ill for cardioscopy to be undertaken. A clinical diagnosis of high blood pressure and heart failure was made, and the aortic diastolic murmur was considered to be the result of relative aortic incompetence. The response to digitalis and mercurial diuretics was poor and the patient died after three weeks in hospital, having developed pyrexia and terminal broncho-pneumonia.

Post-mortem examination (Dr. W. W. Woods). There was great œdema of legs, thighs, and back. In the skin of the upper part of the back, between the shoulders, and the lower part of the back of the neck, there were many confluent dilated veins, more numerous on the right side than on the left. The heart, which weighed 624 g. (22 ounces), showed moderate hypertrophy without dilatation of the left ventricle, slight dilatation of the left auricle, considerable hypertrophy and dilatation of the right ventricle which formed the apex of the heart, and even greater dilatation of the right auricle, particularly of its appendage. In the right auricle, at the junction of the anterior and septal cusps of the tricuspid valve, there was an orifice (0·7 cm. in diameter). The opening was fimbriated and the irregular fringe projected about 1 cm. above the surface of the valve (Fig. 1). A probe, passed through this opening, appeared at the bottom of the anterior sinus of Valsalva: the opening here was on

FIG. 1.—Interior of the right auricle. The opening of the cardio-aortic fistula is seen with a fimbriated and irregular fringe projecting about 1 cm. above the surface of the valve. The fimbriated opening (indicated by an arrow) is at the junction of the anterior and septal cusps of the tricusped valve.

FIG. 2.—The aorta and aortic valves, showing the cardio-aortic fistula (indicated by an arrow) at the bottom of the anterior sinus of Valsalva.

the left side of the sinus and was 1 cm. in diameter (Fig. 2). The communication between the aorta and auricle was lined by smooth endocardium; there were no vegetations or thickenings. There were no other congenital abnormalities. The aortic valve was competent and measured 8·2 cm. in circumference. The pulmonary valve measured 10·5 cm. in circumference. All valve cusps were normal. Apart from one small button in the anterior descending branch, the coronary arteries were free from atheroma. There was moderate atheroma of the aorta. The pulmonary artery and its branches in the lungs were dilated and there were numerous fat flecks in the larger branches. The lungs showed œdema and congestion, and bronchopneumonic consolidation involved the upper half of the left lower lobe. The right thorax contained 70 c.c. (2·5 oz.) of clear fluid and the left contained 42 c.c. (1·5 oz.). The abdomen contained 370 c.c. (13 oz.) of clear fluid. The liver was enlarged and showed areas of slight central congestion. The spleen was slightly œdematous and congested. The kidneys were firm from back-pressure congestion; there was no marked fibrosis, but the arcuate arteries were slightly thickened. The changes at necropsy were consistent with hypertensive heart failure and the effects of the cardio-aortic fistula.

Discussion

Localized defects of the aortic septum may lead to abnormal communication between the base of the aorta and the pulmonary artery or the pulmonary conus. When the opening is from the aorta to the right ventricle or right auricle it usually results from the rupture of a congenital aneurysm of one of the sinuses of Valsalva. Such an aneurysm arising from the posterior sinus of Valsalva and projecting into the right auricle and rupturing there a few hours before death was described by Goehring (1920). He reviewed five similar cases that had been reported; in only one case did an aneurysm from the anterior sinus lead into the right auricle. Abbott (1919) described a case in which an aneurysm of the right sinus of Valsalva had ruptured into the pulmonary conus. A correct clinical diagnosis was made in this case in which a continuous roaring murmur was heard; its accompanying vibration was so marked that it shook the bedclothes. In Goehring's case a loud rough diastolic murmur was heard in the third intercostal space to the left of the sternum and there was a systolic murmur also. Sudden collapse of the patient six hours before death was presumed to correspond with the rupture of the aneurysm. Brown (1939) mentions two cases of sudden death in young people resulting from rupture of an aneurysm of the sinus of Valsalva, into the right auricle and ventricle in one case and into the pericardial cavity in the other.

In the case reported here it is probable that the fimbriated opening was the outcome of a ruptured congenital aneurysm, but there was no episode in the patient's history that would indicate when the rupture took place. The fistula satisfactorily explained the presence of the diastolic murmur and the prominent venous congestion. The case is of further interest because of the age the patient had attained without incurring the most serious and common complication of such congenital lesions—bacterial endocarditis.

Summary

An unusual case is recorded of an elderly man who showed at necropsy a cardio-aortic fistula, which led from the bottom of the anterior sinus of Valsalva to the right auricle near the tricuspid valve.

This communication illustrates a rare cause of a diastolic murmur heard along the right border of the sternum.

I would like to thank Dr. Horace Evans for permission to publish this case, Dr. William Evans for his help and advice, and Mr. John King for the photographs.

References

Abbott, M. E. (1919). *Contributions to Medical and Biological Research, New York*, **2**, 899.
Brown, J. W. (1939). *Congenital Heart Disease*, London.
Goehring, C. (1920). *J. Med. Research*, **42**, 49.

MERCURIAL DIURETICS

THE ADDITION OF MAGNESIUM SULPHATE TO PREVENT THE TOXIC EFFECTS OF THEIR INTRAVENOUS ADMINISTRATION

BY

IGNACY PINES, ANTONIO SANABRIA, AND R. T. HERNANDEZ ARRIENS

From the Department of Cardiology, Central University of Venezuela

Received October 30, 1944

The importance of mercurial diuretics in the treatment of heart failure has been obvious ever since the discovery of these useful drugs. Subsequent studies have explained to some extent the mechanism of their action. The relief afforded to the heart by the administration of mercurial diuretics in cardiac failure depends on the elimination of œdema, on the decrease of the volume of circulating blood, and sometimes on the fall of the arterial blood pressure. The interaction of these factors throws much less burden upon the exhausted heart. The disappearance of œdema is itself of great importance. This is accompanied, as has been shown by Blalock *et al.*[1], by the decrease of the volume of blood flow needed by the tissues for their metabolic requirements, and a reduction of the mechanical resistance of the tissues to the flow of blood. The fall of blood pressure noted many times by various observers after the improvement of the circulation, which can perhaps be attributed to the diminution of local venous pressure in the kidney (Corrigan and Pines [2]), acts also in the same direction.

To these must sometimes be added an increase in the functional capacity of the heart muscle because of a decrease in the heart œdema itself, as well as the complicated effects of the relief of congestion of other important organs. So, for instance, the diuresis after mercurial diuretics has a very favourable influence upon cardiac dyspnœa and on the congestion of the lungs. Also the abdominal circulation is much improved because there is less engorgement of the liver. Finally, the disappearance of the discomfort to which the patient with heart failure is exposed, the recession of insomnia and of the cough, the improved absorption of certain nutritional factors and in particular of vitamins, the decrease of basal metabolism, all these and other factors make the improvement due to diuresis induced by mercurial diuretics even more striking.

It is not surprising, therefore, that mercurial diuretics are highly rated amongst other drugs used in heart failure. According to Thomson,[3] Marvin,[4] and others their diuretic effects are often as great with digitalis as without it. Fishberg [5] points out that they not only " supplement the digitalis, but instances are not rare in which mercurials are decidedly more efficacious than digitalis " itself. Withering's discovery is considered generally to be the opening of the first chapter in the efficient treatment of heart failure. There cannot be the slightest doubt, then, that the introduction of mercurial diuretics by Saxl and Heilig [6] has marked the beginning of the second period.

The diuretic properties of mercurials were known, of course, even before the papers of Viennese authors appeared. According to Goodman and Gilman,[7] calomel was used by Paracelsus for this purpose in the sixteenth century. Later on, Jendrassik,[8] in 1886, confirmed the beneficial action of this drug upon patients suffering from cardiac dropsy. Fourneau and

Mellville [9] quote the important investigations of Blumenthal and Oppenheim [10] in which several organic and inorganic mercury compounds were studied and demonstrated, perhaps with the exception of mercury chloride, to possess various grades of diuretic activities. Nevertheless, the true interest of clinicians was aroused only by the introduction of mercury salicylate by Saxl and Heilig [6] and only since then the mercurial diuretics have been commonly used in the clinic for the treatment of cardiac dropsy and other diseases accompanied by the accumulation of important amounts of fluid in the tissues. This was due perhaps to the fact that, as was proved by the last mentioned authors, mercury salicylate or merbafen and even the less toxic salyrgan or mersalyl, produce much more pronounced diuresis than other mercury compounds, as for instance, mercury chloride or mercury succinate.

Since the beginning of the era of the mercurial diuretics, however, it has been known that they are not without certain toxic influence. Saxl [11] was clearly opposed to the administration of these diuretics in cases of severe anæmia, cachexia, fever, or diarrhœa, and advised great prudence in dealing with patients whose blood pressure was above 200 mm. The most pronounced toxic effects were, of course, registered at the sites of the excretion of mercury from the body, i.e. the kidney and colon. The essence of the diuretic action itself consists chiefly, as was demonstrated, of the irritation of the renal tubules by the mercurial ion and " represents a very early stage of the toxic action of mercury on the kidney " (Goodman and Gilman [7]). The administration of mercurial diuretics is accompanied sometimes, therefore, by the appearance in the urine of hyaline and granular casts, albumin, leucocytes, and erythrocytes, and by more or less marked degeneration of the epithelium of the tubules. The effects on the digestive apparatus, on the other hand, are also those of typical mercury poisoning and appear in the form of stomatitis, salivation, and hæmorrhagic colitis. These changes, if present before the administration of mercurial diuretics, were automatic contra-indications against their use. Nevertheless, with greater experience acquired in dealing with these drugs, the initial precautions taken in their administration were to some extent relaxed. Amongst kidney diseases, cases of nephrosis or amyloidosis react sometimes beautifully to mercurial diuretics and no physician will hesitate to use them to free the patient from the great discomfort and danger of anasarca. The signs which were originally considered as strong contra-indications, as for instance, albuminuria, heightened blood pressure, presence of increased amount of casts and red blood cells in the urine, increase of non-protein nitrogen in blood, are known to accompany sometimes the stasis kidney and do not exclude *a priori* the use of these valuable drugs. The only important contra-indications that remain from the renal point of view are an inflammatory disease of the kidney, i.e. an acute or chronic glomerulonephritis, and malignant nephrosclerosis (Scherf and Boyd [12]), and the only sign which deserves much attention and suggests prudence is the presence of diminished specific gravity of urine as a possible manifestation of renal insufficiency. Moreover, in recent times it has been proved that in most cases even of chronic nephritis there was no " evidence that the kidneys have been injured by the mercury " (Marvin [4]), and some authors (Petersen,[13] Tursz,[14] and Pines [15]) used successfully mercurial diuretics in the treatment of desperate anuria cases. In these latter instances the action of mercurial diuretics can be perhaps compared to the water treatment of Volhard [16] of some anuric or severely oliguric patients with acute glomerulonephritis in which the drinking of 1500 c.c. of water within one-half hour can force the existent renal block (Fishberg [17]).

Concerning the digestive tract the only true contra-indication is the presence of ulcerative colitis (Marvin [4]). The really severe colitis with diarrhœa and bloody stools as the consequence of the administration of new mercurial diuretics is extremely rare and does not take place if the renal function is not impaired. A slightly increased number of stools following the injection, on the other hand, though perhaps a warning signal, is not by itself a contra-indication to the further use of the drugs. And stomatitis and excessive salivation according to Stokes [18] and De Graff and Nadler [19] are not always very reliable signs of mercurial intoxication and depend to the same extent " on the bacterial flora of the mouth and incidental conditions as on the dose of mercury that the patient is receiving.

Unfortunately, together with this recent evidence proving that the use of mercurial diuretics might be entirely safe in cases that previously were considered as not fit to receive even a small quantity of these drugs, new toxic reactions have been described, some of them connected with the drug itself and some with the diuresis that follows its administration. Moreover, some of these toxic reactions can be foreseen and eventually avoided or treated successfully; some of them, however, are unforeseeable and can lead to death in a most rapid and unexpected way.

Many of the alarming or even fatal reactions occur relatively late after the injection of the mercurial diuretic. This by itself indicates the existence of a stronger connection with the diuretic effect than with the mercurial diuretic itself. Fishberg [17] describes three fatal circulatory collapses developed between 8 and 14 hours after the intravenous injection of salyrgan to patients with coronary thrombosis. He attributes the fatal result to the sudden mobilization of a large amount of fluid into the blood stream with the exhaustion of the overburdened heart. Such an explanation is obviously open to certain doubts. The diuresis after the injection of mercurial diuretics starts relatively soon, about 2 to 3 hours after administration and ceases 9 to 21 hours afterwards. Taking into consideration the late occurrence of the fatal reaction and its peripherical character, it is more plausible to assume that the considerable dehydration and diminution of the circulating blood volume was the trigger mechanism of the collapse. Many authors mention dehydration and hæmoconcentration, together with a negative chloride balance as a result of the administration of mercurial diuretic in spite of the persistence of œdema (Degraff and Nadler [19]). Some years ago Fourneau and Mellville [9] attributed, in an experimental study, the chronic intoxication following the use of mercurial diuretics to " some derangement in the animal's water metabolism rather than to associated nephritis." Degraff and Nadler [19] point out that the deficiency of salt interferes with the excretion of water and can provoke the mercurial poisoning due to the incomplete elimination of the drug. The same authors quote Hines [20] as well as Evans and Paxon [21] as representing the opinion that azotæmia appears rather as a consequence of the rapid elimination of great quantities of œdema fluid than of the damage suffered by the kidneys from the mercury. Symptoms of chloride depletion are generally seen after the copious diuresis following mercurial diuretics. Sometimes these are relatively mild and the patients complain of weakness and of pains, particularly in the calf muscles. Other times a severe picture of great chloride depletion, comparable to heat prostration or pernicious vomiting with apathy, somnolence, severe mental symptoms, and eventually death, can develop.

Another type of alarming or fatal reaction following mercurial diuresis can be related to digitalis toxicity. Since 1931 there have appeared various studies indicating that the œdema fluid of digitalized patients can contain large quantities of this drug and produce even toxic reactions when the œdema fluid finds its way rapidly into the blood stream during mercurial diuresis. Biological methods were used in these studies and the authors have proved on hearts of frogs and cats that the œdema fluid of digitalized patients is rich in digitalis or digitalis-like substance. Degraff and Nadler [19] point out that their experience is in accord with these studies and that symptoms of digitalis intoxication appear even when the patients had not received digitalis for several days. Personally we have seen many cases in which toxic symptoms have developed, which could be attributed to redigitalization depending on mercurial diuresis, and agree with them that some precautions must be taken before giving mercurial diuretics to fully digitalized patients. It is, however, worth while to stress that some authors consider that the evidence with respect to the redigitalization which occurs when the œdema fluid enters quickly into the blood stream is not complete and that toxic symptoms can depend as well on many other factors, as for instance, the loss of large quantities of sodium base which gives rise to prostration or a shift of the acid-base equilibrium towards the alkalosis with all its symptoms, such as nausea and vomiting.

Finally a copious diuresis leads sometimes to the fall in serum sodium or calcium. A fall in serum calcium was noted by some observers and others have reported spontaneous tetany development after mercurial diuresis, though this latter was not always accompanied by the diminution of calcium in serum. Degraff and Nadler also mention that grand mal attacks have been attributed in epileptics sometimes to mercurial diuresis.

The careful analysis of other toxic symptoms or signs that appear after mercurial diuretics proves that some of them depend rather on the drug itself than on the diuresis, and that the causal mechanism of others is relatively uncertain. To this latter group belongs perhaps the delayed reaction as described by Wexler and Ellis [22] in the form of typical asthma attacks or pulmonary œdema. Especially the pulmonary œdema can be thought to depend on a great quantity of fluid entering rapidly into the blood stream and creating an unsupportable burden for the exhausted heart. Both their cases, which developed pulmonary œdema 120 and 80 minutes respectively after the intravenous injection

of 2 c.c. of mercupurin, were in the state of cardiac failure, and this seems to speak in favour of such a comment. On the other hand, the pulmonary œdema can be attributed to the toxic effect of mercury upon the heart muscle, and the bronchial asthma to a manifestation of an allergic reaction or of an idiosyncrasy.

Hypersensitive reactions are also well-known from other observations and appear in various forms. About two years ago Fox, Gold, and Leon [23] described a case in which the injection of mercupurin and the administration of mercurin by rectal suppository, although the first 60 injections were well tolerated, led invariably to a severe reaction with fever, rash, nausea and vomiting, thoracic constriction, paresthesias, and swelling of the lips. The reaction developed invariably even when the dose of mercupurin was very small and contained only 4 mg. of mercury, although the second phase of this reaction consisted of signs characteristic of mercury poisoning, i.e. ulcerative stomatitis. The authors conclude rightly that the reaction was not dependent on the liberation of an ionized mercury because there was no hypersensitiveness to other organic or inorganic mercury compounds, whose administration produced marked diuresis with only a negligible reaction or without any reaction at all.

In the same year Higgins [24] described a similar case in which the hypersensitive reaction manifested itself one hour after an intravenous or intramuscular injection of mercupurin under the form of a severe chill, fever, dyspnœa, cyanosis, rapid fall in blood pressure and prostration, all of these symptoms and signs developing in rapid succession. The author points out he excluded the possibility of any cardiorespiratory lesion by the absence of any electrocardiographic evidence and by rapid disappearance of all these disturbances. According to him the fact that the reaction did not appear after three previous injections and that it bore some similarity to the reactions encountered after the administration of arsenicals supports the view that the reaction was of an anaphylactic type. He quotes some reported fatalities that occurred after intravenous injections of mercurial diuretics and not seeing any material difference between his experience and the reactions reported, suggests a new investigation of the toxicity of mercurial diuretics. He did not take into consideration apparently that the reactions described in other cases appeared only after the intravenous injection of the drug, that they manifested themselves much sooner after the injection had been effected, and that all available clinical evidence pointed to a cardiac character of such reactions described by other authors. Degraff and Nadler [19] collected other hypersensitive reactions and mention among others, cutaneous eruptions in the form of urticaria, small reddish spots or purpuric areas, morbilliform and scarlatiniform erythæma, chills, fever, and even reactions resembling a state of shock with sweating, cyanosis, collapse, and urinary suppression. They quote in this respect the investigations of Wilson [25] who demonstrated by patch tests that these reactions may be of an allergic character and the observation of Parent [26] that the individual susceptibility plays in the development of these reactions an important rôle.

All these reactions analysed above have been known for a long time, and have been connected with mercurial diuretics by all authors. Many times they could be foreseen or even avoided, and generally they appeared in lesser or greater degree independently of the route of administration. Moreover, the mechanism of these reactions is in many cases well known as was previously said. Also, the rôle of the kidneys in this respect has been thoroughly considered, and the contra-indications to the use of mercurial diuretics in some renal diseases precisely established. The same is true of the metabolism of salts and water, and it is well known that both of these factors must be carefully watched when mercurial or other diuretics are being given. With reference to redigitalization, there was always a certain difference of opinion, but in the main the diuretic mercurial is injected before the full digitalization of the patient is reached, or the quantities of mercurial are small, around 0·5 c.c., in order to avoid a violent reaction. Although hypersensitive reactions cannot be foreseen, even in these cases certain precautions can be taken by diminishing the initial dose of the drug, or by changing one preparation for another, or finally by adding certain substances like calcium gluconate to the mercurial diuretic before injection. Altogether, the known mechanism of reactions, the thorough analysis of contra-indications, and the precautions used in the injection of mercurial diuretics have brought about a relatively great degree of safety for the patients in the use of these drugs, and even when the reactions developed sometimes after the injection, they were of minor significance, and only extremely rarely alarming or fatal. There is, however, another type of toxic reactions appearing after mercurial diuretics that are completely different from all other reactions considered above, and the mechanism of which has only lately begun to be better understood and known.

The main features of this new type of reactions are as follows: (1) They manifest themselves in the clinic only after the intravenous route of administration, though there are certain suspicions in respect also to peritoneal route. (2) They appear very soon after the injection is over, generally from a few seconds to 5 or at most 10 minutes, and stop within a very short time if they are not fatal. (3) There is experimental and clinical evidence that these reactions happen because of disturbances in the specific heart musculature and perhaps also in the active musculature of the ventricles. (4) The peripherial vascular collapse was not observed during these reactions and, therefore, they are probably not of an anaphylactic nature (Wexler and Ellis [22]). (5) The reactions are often severe and in great proportion they lead to immediate death. (6) Relatively small quantity of the drug or its high dilution does not always prevent the appearance of disturbances (Degraff and Nadler [19]). (7) It seems that the reactions are more severe in the presence of considerable heart failure, though many of them have been described without heart insufficiency at all (cases of nephrosis). (8) They appear sometimes after the first injection, but sometimes also after the patient has received as much as 164 c.c. of mercupurin (Wexler and Ellis [22]); sometimes all previous injections produce rather benign symptoms as in both fatal cases of Wexler and Ellis, or the previous injections are supported without any untoward symptoms as happened in Wilson's [25] cases. (9) Sometimes all measures taken including epinephrine injections cannot prevent death (for instance, Carrillo's [45] case), but sometimes epinephrine injections or other measures like morphine and oxygen seemed to be helpful (fourth case of non-fatal immediate reaction of Wexler and Ellis). (10) The reactions appear with particular frequency after esidrone and mercupurin injection, though sometimes the exchange of mercupurin for salyrgan does not prevent the reaction (first case of Barker, Lindberg, and Thomas [27]).

This new type of toxic reaction after the intravenous administration of mercurial diuretics and in particular after mercupurin or esidrone seems so dangerous to everybody who has seen it (the senior author's 2 cases) that some authors are already demanding a re-examination of the whole subject of mercurial diuretics (Higgins [24] and Friedfeld, Kissin, Modell and Sussman [28]), some recommend great prudence in intravenous administration (Carrillo [45]), and some recall that the diuretic response after intramuscular injection is often sufficiently abundant and that after intramuscular injection no fatalities as yet have been reported, or directly recommend the intramuscular route.

It is true that, as Wexler and Ellis [22] point out, the frequency of severe or fatal reactions after the intravenous administration of mercurial diuretics is relatively low. In the reports available to us we find 26 cases analysed by Degraff and Nadler [19] in 1942 beginning from Redlich's [29] cases reported in 1926, i.e. for a period covering 16 years. To these must be now added 2 cases of Levin [30] quoted by Carrillo,[45] his own case, 2 cases seen by the senior of the authors, and 2 fatal and 5 alarming (immediate) non-fatal reactions encountered by Wexler and Ellis during 16 months in the Boston City Hospital. Though, perhaps, the statement of Degraff and Nadler in respect of the lowness of toxicity of mercurial diuretics as compared with the toxicity of arsphenamines still holds good, we do not believe that in the case of mercurial diuretics the state of the literature actually reflects the real toxicity of these drugs. This depends in part on the fact that the fulminant reactions have been known and understood only a relatively short time, in part because until ten or twelve years ago, the less toxic salyrgan and neptal were used instead of the more toxic novurit, esidrone, and mercupurin, in part because in the early years of mercurial diuretics intramuscular injections were used much more frequently than intravenous injections, in part because not all fatal reactions were attributed to the mercurial diuretics as the patients were in a very bad shape at the moment of injection, and finally in part because of unknown reasons.

The use of intravenous injections of mercurial diuretics in the treatment of heart disease is raising problems of increasing importance. Many authors (Fishberg,[5] Levine [32]) stress the efficiency of intravenous injections even when the intramuscular route does not give a

good diuresis, but already some hesitate very much before choosing this route. For example, Goodman and Corsaro [33] refer to the toxicity of mercurial diuretics by intravenous injections, saying that only the intramuscular route was used in their study. Such an attitude is even more justified by the results of experimental studies.

After the initial experiments of Dresser [31] in 1893, Mueller, Schoeller, and Schrauth [34] described in 1911 an acute type of intoxication with mercury compounds which led to an immediate death in cats. In 1922 Salant and Kleitman [35] performed their perfusion experiments with inorganic and organic mercury salts on a turtle heart and showed that a mercury compound independently of its anion produces disturbances of heart action particularly of the cardiac rhythm. The time at which these appeared depended on the concentration of the mercury salt, though when the experiment was carried on for long enough " delirium cordis " developed with dilutions as high as 1/10,000,000. They showed, too, that in dogs, " delirium cordis " resulted from the intravenous injections of inorganic mercurial salts and mercurochrome; and Salant and Kleitman's results with cats and dogs were similar to those obtained in more recent studies on the toxicity of organic mercury compounds. In 1923 Hatcher and Weiss [36] attributed the emesis appearing after the intravenous injections of mercury chloride to direct reflexes from the heart. In 1926 Jackson [37] studying the pharmacologic action of organic mercury compounds on the heart reported that 5 c.c. of a 2 per cent solution of salyrgan (about 100 mg. of salyrgan and 39·6 mg. of mercury) were producing regularly within 3 to 5 minutes the death of normal dogs through ventricular fibrillation. In 1929 McCrea and Meek [38] proved that larger doses of mercury compounds produce pathological rhythms of the animal heart. In 1931 Fourneau and Mellville [9] confirmed the results of Mueller, Schoeller, and Schrauth [34] in respect of the " hyperacute fulminant " type of intoxication immediately after the intravenous administration of mercury compounds, but though " no definite lesions could be found in the central nervous system," they attributed the intoxication to the action on the central respiratory mechanism. In the same year Salant and Nagler [39] when studying the effect of calcium and potassium on cardiac reactions to mercury, and making use of the isolated frog heart with Straub's method, found that mercury (bichloride) in concentrations above 1/500,000 in normal Ringer acted upon the conduction system as well as upon the active musculature of the heart producing the decrease of force and frequency of contractions and a certain irregularity of cardiac action; the cardiac resistance to mercury was considerably diminished in the hypodynamic heart, and also by interrupted treatment with mercury. After giving a solution 1/100,000 within about 30 minutes in certain experiments there was a progressive depression of the heart, whereas in others, the heart action was becoming weaker and irregular, extrasystoles and heart block manifesting themselves and persisting for a long time. The auricle was much more resistent against mercury than the ventricle, and calcium protected the heart from the toxicity of mercury compounds partially perhaps by decreasing permeability of cellular membrane, while potassium and mercury often showed synergism in their action upon the heart muscle.

The results of those older investigations have been fully confirmed by more recent studies. Chastain and Mackie [40] in 1940 administering large intravenous doses of esidrone to normal dogs under barbiturate anæsthesia observed within 12 to 15 seconds after the injection deviation of the T waves, followed by ventricular flutter, fibrillation, and death. One year later Johnston [41] showed similar results of intoxication with mercury salts, but added that the isolated turtle heart as well as the heart of the intact cat could recover if subjected to after-treatment with sodium thiosulphate. In 1942 Barker, Lindberg, and Thomas [27] in an extensive study gave various mercurial diuretics intravenously to 30 normal dogs with and without intravenous barbital anæsthesia. Death was produced always by a particular pattern composed of depression of T waves, ventricular extrasystoles, ventricular tachycardia, and ventricular fibrillation. The results were exactly the same in the anæsthetized animals as in 4 vagotomized animals, in 2 animals with the cervical cord and both vagi severed, and in instances of an isolated perfused heart. From Fig. 1, 2, and 3 of their paper it is seen that the authors used in those experiments 2 c.c. of salyrgan, 2·2 c.c. of salyrgan and theophylline, and 1·4 c.c. of mercupurin. Otherwise the equivalent amounts of organic or inorganic mercury compounds were administered. The authors feel that " the mercury ion acts directly on the ventricular muscle to produce ventricular fibrillation and death."

In the same year another excellent study was presented by Degraff and Lehman,[42] in which many pertinent data with reference to the acute toxicity of mercurial diuretics were firmly established. In experiments on cats and using the scheme similar to the proposed U.S.P.XII cat assay for digitalis the authors found the mean lethal dose for every mercurial diuretic frequently used by the medical profession. This mean lethal dose is the smallest for esidrone and greatest for salyrgan-theophylline, esidrone without theophylline, salyrgan, mercurin, and mercupurin occupying intermediary places

between those two extremes. Moreover, they proved that the previous administration of digitaline Nativelle, aminophylline, ammonium chloride, and soluble phenobarbital had no influence upon the mean lethal dose, and that even a slow rate of intravenous injection of mercurial diuretic to man did not give a guarantee against a lethal reaction. Some suggestions in respect to the slight protective action of a great dilution of the drug were also made, but one animal out of three died at a dilution of the drug as high as 1/25. Finally the conclusion was drawn that the lethal reaction is due exclusively to the cardiac action of the drug, the terminal event being ventricular fibrillation or respiratory failure depending on circulatory failure, and that the more gradual intravenous administration or the intramuscular injection of considerable quantities of mercurial diuretic produce successively the T wave changes accompanied by the fall of arterial and venous pressures, rapid ventricular tachycardia, and in case the heart does not recover, death through ventricular fibrillation or complete respiratory failure because of fall of arterial blood pressure. The authors also point to some experimental evidence that epinephrine can improve the heart poisoned by mercury, whereas ergotamine rather increases the toxicity of these drugs, and that the favourable influence of sodium thiosulphate and sodium formaldehyde sulphoxylate upon the heart disturbances provoked by the injection of mercurials must be further investigated.

In addition to these investigations Wexler and Ellis [22] state that there is strong clinical evidence that in man the mechanism of lethal superacute or fulminant reaction to the intravenous injection of mercurial diuretics is exactly the same as in case of animals, and that " at present there is no known way of preventing fatal reactions."

In conclusion, the mercuric ion liberated from organic mercurials produces abundant diuresis through its action upon the renal tubules, but simultaneously in certain doses, and if appearing rapidly in the blood stream of a mammal, it provokes serious disturbances in the conduction system of the heart as well as in the musculature of the ventricles. Previous research has established in general lines the mechanism of this phenomenon, but certain details are still lacking, and even more important no pertinent method has been indicated in order to avoid fatal or alarming reactions in man, especially when we are dealing with serious lesions of heart muscle. It seems of great urgency and importance, therefore, to find out if certain changes introduced in the chemical composition of mercurial diuretics or certain substances added or incorporated into them could prevent fatal reactions in human beings, and thus re-establish the safety of intravenous injections. If certain substances must be added to mercurial diuretics, to prevent fatal reactions they should, according to us, possess three other following qualities: viz., they should not diminish the diuretic qualities of mercurials but should if possible increase them by a synergistic action; they must be innocuous in the doses recommended; and finally, they must mix well with mercurial diuretics without forming a precipitate.

The search for such a substance or substances together with the effort to increase our knowledge in respect of the mechanism of fatal reactions was the principal purpose of the present study.

Method

Dogs were used for the present experiments. In all cases we applied general anæsthesia through the intravenous injection of pertinent amounts of somnifen Roche, because as was proved by Barker, Lindberg, and Thomas,[27] the phenobarbital anæsthesia does not change the character of reaction due to injection of mercurial diuretics. Moreover, as the respiratory failure is only a secondary phenomenon and follows disturbances in heart action, artificial respiration was used in nearly all experiments. In a few, in which we did not open the chest of the animal and did not need, therefore, artificial respiration, the results were just the same as in all others. After the trachea was opened and artificial respiration applied, we proceeded in most experiments to open the chest in the usual way, trying to avoid all unnecessary hæmorrhage. The pericardial sac was opened by a broad triangular dissection and its borders fixed to the chest walls. The disturbances of heart action were observed directly

and registered by means of electrocardiogram taken sometimes in the first, sometimes in the second lead, and sometimes in both. The Cambridge string electrocardiograph was used throughout.

The experiments consisted in partially intravenous and partially intracardiac injections of different amounts of esidrone. The injections were given sometimes into the cavity of the right auricle, sometimes into the cavity of the left ventricle or auricle, and sometimes into the jugular vein which was dissected beforehand and left free for this purpose. We were unable to observe any marked difference in the influence of esidrone upon the heart depending on the different place of injection. In the beginning by intracardiac or intravenous injection of 4 c.c. of esidrone we provoked the appearance of ventricular tachycardia followed within a few seconds by ventricular fibrillation. Later on, we convinced ourselves that the above-mentioned disturbances followed by a complete standstill of heart ventricles could be provoked in a dog of between 6 and 14 kg. of weight by an injection of only 2 c.c. of esidrone, though the ventricular fibrillation and complete heart standstill appeared a little later than by using 4 c.c. Nevertheless, the difference of time was only of seconds or of minutes, because even when 2 c.c. of esidrone were injected, the ventricular fibrillation appeared at most within 2 to 3 minutes after injection. At the end of the first phase of our experiments we injected intracardially or intravenously different amounts of 20 per cent solution of sulphate of quinine. This last drug not only did not hinder the appearance of ventricular fibrillation but it can be said that in all three experiments in which the sulphate of quinine was injected almost at once after the esidrone injection, ventricular fibrillation manifested itself at once, i.e. even earlier than was expected from previous experiments with esidrone. Later on we proceeded to inject magnesium sulphate after the full content of esidrone ampoule, i.e. 3 c.c. had been used. This method was changed for the simultaneous injection of magnesium sulphate with esidrone. In the beginning of the magnesium sulphate part of our study 2 c.c. of a 20 per cent solution together with 2·3 c.c. of esidrone were used tentatively. The dose of magnesium sulphate seemed too high, however, because, though the appearance of ventricular fibrillation was much delayed or did not produce itself, the cardiographic changes in respect of the disturbances of auriculo-ventricular and intraventricular conduction were even more marked than in the case of esidrone injection only. We observed also that when enough magnesium sulphate (10 c.c. of 20 per cent solution) was injected even after the esidrone was used, the heart would stop suddenly because of the complete cessation of its automatic function but without having passed through the phase of ventricular fibrillation. On the base of such and similar observations and reasonings the proper dose and timing of the magnesium sulphate injections were arrived at. In the last part of our experiments we were injecting the full amount of esidrone ampoule together with 0·5 c.c. of a 20 per cent solution of magnesium sulphate. The injections were effected with half-hour intervals between one another and no persisting heart disturbances were noted. Using this last method as many as seven times the lethal dose as established in previous experiments could be injected intravenously or intracardially and the heart still returned to the sinus though a little slower rhythm with disappearance of auriculo-ventricular and intraventricular block.

Results

As already stated, we were able to confirm the experience of previous authors in respect of the unfavourable effect of certain doses of mercurial diuretics introduced rapidly into the blood stream upon the conduction system and the active musculature of the ventricles.

No effects upon the respiratory centre could be observed, however, because we were using artificial respiration, as we believe together with Degraff and Lehman[42] that the changes in the respiratory centre during the course of fulminant intoxication with mercurial diuretics are completely secondary and depend in the first place on the fall of arterial blood pressure.

The doses administered to dogs chosen on the base of the mean lethal dose established for normal cats by Degraff and Lehman have proved themselves a little too high because those quantities of esidrone injected intracardially or even intravenously provoked ventricular fibrillation almost at once and did not permit observation of the course of intoxication. So, for instance, in one experiment the intracardiac injection of 4 c.c. of esidrone to a dog of 17 kg. produced immediately intraventricular block and a few seconds later irreversible ventricular fibrillation, although the lethal dose for this dog as calculated on the base of mean lethal dose established for cats by Degraff and Lehman would be 4·08 c.c. of esidrone (Fig. 1). In other experiments when we administered esidrone by the jugular vein similar

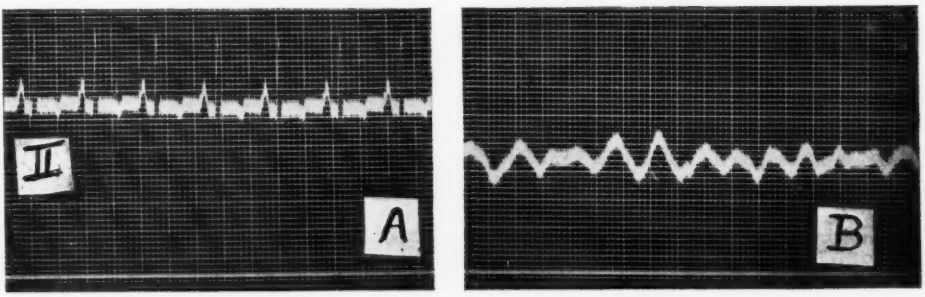


FIG. 1.—(A) Before injection of esidrone: normal rhythm; frequency 136 a minute; P–R, 0·12 sec.; QRS, 0·04 sec.; T negative, 1·5 mm. (B) Instantaneous ventricular fibrillation after injection of 4 c.c. of esidrone.

results were obtained. At the end of our first stage of experiments, therefore, we diminished considerably the dose of esidrone and injected dogs of even above 10 kg. with a quantity of esidrone which varied between 1 and 2 c.c. This was always enough to provoke the fulminant intoxication with ventricular fibrillation appearing within 2 to 5 minutes, thus enabling us to observe better all electrocardiographic changes. This agrees with Barker, Lindberg, and Thomas,[27] who obtained ventricular fibrillation and death by injecting a dog of 7 kg. with a dose of mercurin not higher than 1·4 c.c., although according to Degraff and Lehman's data for cats the lethal dose for this dog should have been 5·8 c.c. We have no other explanation for this fact than the possible influence of barbital anæsthesia used by us as well as by Barker, Lindberg, and Thomas in spite of the fact that these authors did not find proofs for the existence of such a difference, and also perhaps the fact that we were administering the full lethal dose at once, together with the difference between two species.

From this first part of our experiments two other facts are also apparent. The anoxia of heart muscle increases its sensitivity to intoxication by mercurial diuretics, as in two experiments in which the artificial respiration apparatus ceased to work because of some defect of its mechanism, ventricular fibrillation appeared at once, and thus much earlier than we could expect on the base of our previous experience with the same dose of esidrone. This perhaps can explain to some extent why a failing heart and in particular infarcted heart muscle seems to be more sensitive to mercurial intoxication (Fishberg [17]).

Another fact which we observed concerns the development of intoxication. Degraff and Lehman,[42] as well as Barker, Lindberg, and Thomas,[27] describe a particular pattern of mercurial intoxication consisting of early changes of the T wave, followed by disturbances in intraventricular conduction, ventricular extrasystoles, ventricular tachycardia, ventricular flutter and fibrillation, and death. In some of our experiments, however, we were able to observe a more uniform action of mercurial diuretics upon the heart conduction system, as on a parallel line with T wave changes and intraventricular conduction defect, there appeared some disturbance of auriculo-ventricular conduction (Fig. 2). This agrees with the clinical

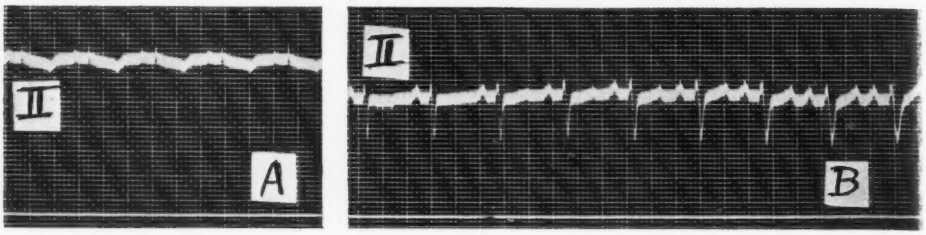


FIG. 2.—(A) Before injection of esidrone: normal rhythm; frequency 111 a minute; P–R, 0·12 sec.; QRS of small amplitude and 0·03 sec. ; T negative, 2 mm. (B) After injection of 2·3 c.c. of esidrone: normal rhythm; frequency 115 a minute; P–R, 0·18 sec.; QRS broad, deformed, with S wave deep in form of staircase (" en marche d'escalier "), and 0·16 sec.; T positive, 3mm. Simultaneous appearance of auriculo-ventricular and intraventricular conduction disturbances after esidrone.

observation of Wexler and Ellis,[22] who in one case of rheumatic heart disease with auricular fibrillation mention the appearance of periods of complete heart block with a ventricular rate around 50 during acute intoxication with mercurial diuretics.

Finally, from the first part of our study it seems that sulphate of quinine not only has no hindering effect upon the development of ventricular fibrillation in the course of intoxication with mercurial diuretics, but on the contrary rather accelerates it, as is well seen from Fig. 3A, B, and C, where the administration of 0·25 g. of sulphate of quinine has, if anything,

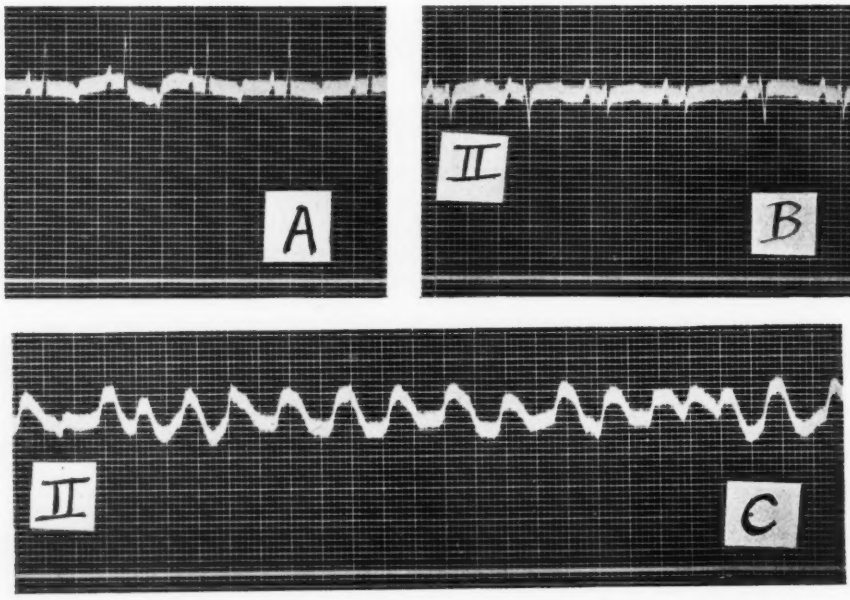


FIG. 3.—(A) Before injection of esidrone: normal rhythm; frequency 120 a minute; P–R, 0·11 sec.; QRS, 0·04 sec.; T negative, 1·5 mm. (B) After injection of 1 c.c. of esidrone: normal rhythm; frequency 120 a minute; P–R, 0·12 sec.; QRS completely changed, of small amplitude, and 0·08 sec.; T positive, 0·5 mm. (C) Instantaneous ventricular fibrillation after injection of 1 c.c. of a 25 per cent solution of quinine.

quickened the mercurial reaction. This effect of quinine and quinidine especially in greater amounts is well known from experience with even healthy heart muscle (Boyd and Scherf,[43] Goodman and Gilman [7]).

From the second part of our experiments the conclusion must be drawn that magnesium

sulphate has a suppressing effect upon the ventricular fibrillation provoked by the administration of mercurial diuretics. This tendency is well seen from one experiment, in which 10 c.c. of a 20 per cent solution administered within 2 minutes after the injection of 2·3 c.c. of esidrone and in a moment when disturbances of intraventricular conduction had already manifested themselves, hindered the appearance of ventricular fibrillation, though the action of the heart ceased suddenly after the short period of considerable disturbances in auriculo-ventricular and intraventricular conduction. The possibility of a kind of synergistic action of magnesium sulphate and of mercurial diuretic in toxic doses upon the conduction system of the heart induced us to diminish greatly the dose of magnesium sulphate and in order to assure a favourable effect, we began to inject this last substance simultaneously with esidrone. In these latter experiments we observed a very favourable action of 0·5 c.c. of a 20 per cent solution of magnesium sulphate upon the course of heart intoxication due to intracardiac or intravenous injection of esidrone. Thanks to this suppressive action of magnesium sulphate in the dose mentioned, we could administer up to seven times the dose which we have every reason to consider as lethal, without any persisting ill effects upon the heart action. This does not mean that 0·5 c.c. of a 20 per cent solution of magnesium sulphate always and totally arrested the reaction due to the administration of a mercurial diuretic in the dose known as lethal. Sometimes the disturbances of the conduction system did not manifest themselves at all after the first dose of 2·3 c.c. of esidrone. Sometimes they did, however, and always appeared after the second 2·3 c.c. dose of esidrone. But they never continued and the heart of the animal after a certain time, generally less than 30 minutes, returned to sinus rhythm, though often slower than before, the ventricular complexes acquiring normal aspect and the T waves returning nearly to their previous shape.

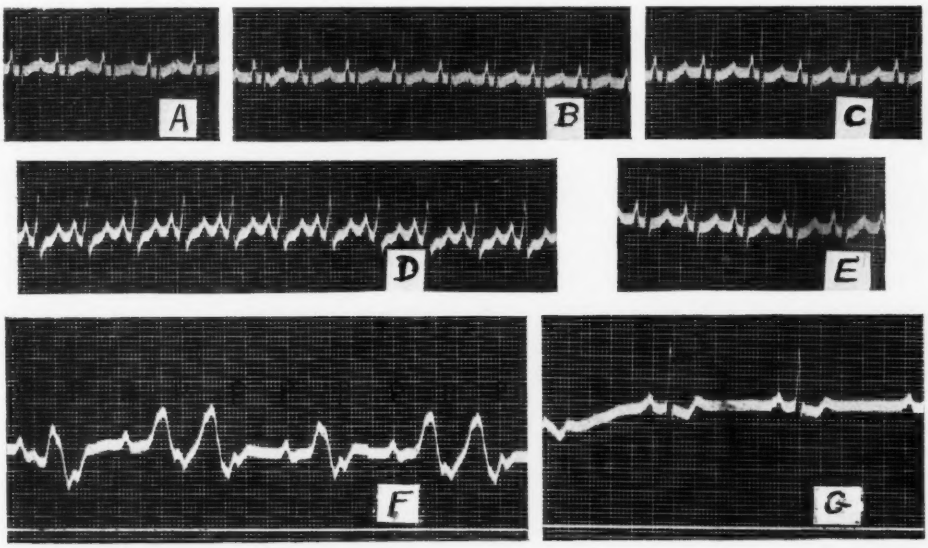


FIG. 4.—Repeated injection of esidrone. All lead I. (A) Before injection of esidrone: sinus rhythm; frequency 143 a minute; P–R, 0·10 sec.; QRS, 0·05 sec.; T positive, 1 mm. (B) Normal appearance after injection of 2·3 c.c. of esidrone and 0·5 c.c. of a 20 per cent solution of magnesium sulphate. (C) The same within 5 minutes after the second injection of the same combination of drugs. (D) After third injection of esidrone and magnesium sulphate: sinus rhythm; frequency 143 a minute; P–R, 0·12 sec.; QRS, 0·12 sec.; T positive, 2 mm. (E) Electrocardiogram returning to its normal aspect within 5 minutes after third injection of esidrone and magnesium sulphate. (F) After sixth injection of 2·3 c.c. of esidrone and 0·5 c.c. of a 20 per cent solution of magnesium sulphate. Complete heart block and atypical ventricular complexes. Auricular frequency 130 a minute. (G) After seventh injection of esidrone and magnesium sulphate: sinus rhythm; frequency 49 a minute; P–R, 0·24 sec.; QRS, 0·08 sec.; T diphasic.

To illustrate better this influence of magnesium sulphate we should like to describe with more detail the course of one of these last typical experiments. The weight of the dog was 12 kg. After a deep anæsthesia, induced through the intravenous injection of 10 c.c. of somnifen, we proceeded to artificial respiration and chest opening in the above described way. The pericardial sac was opened and fixed to the chest borders. The cardiogram is normal in all respects, the heart frequency being 142 a minute (Fig. 4A).

The first injection of 2·3 c.c. of esidrone +0·5 c.c. of a 20 per cent solution of magnesium sulphate did not produce any appreciable changes during half an hour of observation. The second injection of the same combination of drugs, on the contrary, produced the appearance of intraventricular, though not very intensive, conduction defect. Moreover, these intraventricular conduction disturbances lasted for only a very short time, ceasing completely after about 5 minutes, when Fig. 4C was taken. The third injection produced more intraventricular conduction defects accompanied by prolongation of P–R, but even this time the cardiogram returned within 5 minutes to its normal (Fig. 4E). The following fourth, fifth, and sixth injections produced even more accentuated changes in the intraventricular and auriculo-ventricular conduction including complete auriculo-ventricular block and a few times an atypical ventricular complex, but invariably after perhaps a little more time, although well below half an hour, sinus rhythm was re-establishing itself (Fig. 4G). At the end, after 5 hours, the experiment was interrupted without the appearance of ventricular fibrillation.

All experiments done in the same way gave similar results, although sometimes we could induce ventricular fibrillation by repeating at small intervals of time the injections of a dose as high as 4 c.c. of esidrone. The conclusion was drawn, therefore, that magnesium sulphate has a hindering effect upon the ventricular fibrillation due to intoxication of mercurial diuretics, though it does not suppress the ill effects of the injections of excessive doses and generally does not hinder the appearance of some disturbances in the auriculo-ventricular or intraventricular conduction.

Comment

From clinical observation and from experiments upon animals, confirmed also by this study, we can now reconstruct the influence of the mercurial compounds upon the heart muscle. In certain doses they are powerful depressants for the whole of the heart muscle. This action is much weaker upon the higher segments of the heart but increases rapidly beginning from the A-V node. In this respect we can confirm Salant and Nagler,[39] who have proved that the auricle was much more resistant to mercurial compounds than the ventricle, and the recent observations of Barker, Lindberg, and Thomas,[27] that after the ventricular electrical impulses have stopped, the auricles continued to beat in a regular sinus rhythm. We had the opportunity to observe the same phenomenon many times. This does not mean, however, that the mercurial compounds have no influence upon the S-A node or upon the auricular muscle. Simultaneously with the appearance of complete heart block nearly always a small decrease of the auricular rate, and therefore, a slight decrease of the frequency of impulse formation in the S-A node, could be noted. After recovery from mercurial intoxication a slower sinus rhythm is the rule according to the investigations of ourselves and other authors (Degraff and Lehman [42]). This recalls to some extent the direct influence of quinidine upon the S-A node.

The depressive influence of mercurial compounds upon the A-V node is, however, much stronger, as in the case of quinidine or quinine. It was recorded by us many times in the form of latent, partial, or complete heart block and was confirmed by Wexler and Ellis's [22] clinical observation of periods of complete heart block during the recovery from mercurial toxic reaction in a case with auricular fibrillation. Moreover, this depressive action of mercurials upon A-V conduction explains also the mechanism of the appearance of the bundle branch block. According to Pines [44] it can be always questioned whether the asynchronism of contraction of the ventricles is caused by the acceleration of conduction in one bundle branch or its slowing in the other, unless there is strong evidence that we are dealing with a phenomenon or a drug which has a depressing action upon various segments of the conduction system. In the case of mercurials such evidence seems to be furnished by their influence upon A-V conduction.

It is more difficult to explain the mechanism of changes in the T waves recorded by all authors who have studied the mechanism of hyperacute intoxication provoked by mercurial compounds. There was a relatively old report of Jackson [37] that salyrgan acts on the heart through the stimulation of the vagi and that as soon as the vagus control is removed, death ensues, not because of heart failure but because of paralysis of the respiratory centre. On the other hand, as we know from the studies of Samojloff [46] and Rothberger and Winterberg [47] that the vagus stimulation produces T waves of small amplitude, the T wave changes occurring in the early stage of mercurial intoxication might depend on the stimulation of the vagus nerve. This explanation is, however, not very probable. Jackson [37] did his experiments on dogs under ether anæsthesia. Kobacker and Rigler,[48] on the other hand, found on cats in 1929 that ether anæsthesia paralyses the vagus nerve. The same was known from Ruttger's [49] experiments on the heart of the frog. Moreover, Steinfeldt [50] proved that the pulse frequency increases during ether anæsthesia, and Rothberger [51] observed that the respiratory arrythmia due to the central excitation of vagus and so well marked in the morphinized dog, disappears immediately after the beginning of the ether anæsthesia. Finally, Pines,[52] in 1934, demonstrated that this effect depends not so much on the diminution of the effect of acetylcholine, but rather on the partial or complete arrest of the secretion of vagus substance. On the basis, therefore, of these experiments the results obtained by Jackson [37] are open to certain doubts. And still more so because Salant and Kleitman,[35] as well as Barker, Lindberg, and Thomas,[27] demonstrated directly by means of bilateral vagotomy or atropinization that the suppression of the influence of the vagus nerve does not change the action of mercurials upon the heart. The changes of the T waves recorded during the early stages of intoxication with mercurials must be, therefore, attributed rather to the toxic effect upon the active musculature of the heart which is known from the experiments of Salant and Nagler,[39] among others, particularly that the increase of strain on either or both ventricles does not enter into consideration before the mobilization of the peripheral fluid has time to occur.

Concerning the ventricular fibrillation reported and observed by all authors as well as by us as the final result of an acute mercurial intoxication, very little need be added. It is well known that many myocardial depressants and myocardial stimulants alike can produce ventricular fibrillation. Even quinidine itself, which has certain value in preventing and alleviating ventricular fibrillation, when administered in excessive doses results in ventricular fibrillation in experimental animals (Katz [53]). Mercurial compounds probably act in a similar way. As a matter of fact we have found a certain synergism between the influence on the heart of large doses of quinine and of mercurial compounds in the later stages of acute mercurial intoxication.

The action of magnesium sulphate in preventing the lethal effects of acute intoxication with mercurial diuretics, must, on the other hand, be considered separately as it is of considerable importance, practically and theoretically.

Magnesium is apparently indispensable for life of the mammals and plants (Goodman and Gilman [7]). Its concentration in human serum is according to current opinion between 2 and 3 mg. per 100 c.c., and in red corpuscles about 4 mg. It is interesting to note its high concentration in cardiac muscle and its fall in cases of cardiac failure. According to Harrison [54] the left ventricle of the normal cardiac muscle contains about 20 mg. of magnesium, whereas the same ventricle of patients who died from congestive heart failure contained only 16 mg. of magnesium per 100 g. of fresh tissue. Pharmacologic properties of magnesium salts have been studied for a long time. Smith, Winkler, and Hoff [55] mention in their paper that the results of their investigations in respect of the action of magnesium on the mammalian heart are in agreement with older experiments of Hay [56] effected in 1882 and relatively more recent investigations performed by Matthews and Jackson [57] in 1907. With reference to the influence of magnesium sulphate on the mammalian organism there was particularly fruitful research connected with the efforts of Meltzer and Auer [58] and of other authors in order to introduce this drug for general and local anæsthesia. It has been found that parenteral administration of magnesium sulphate induces general anæsthesia (Meltzer and Auer); that there is a certain synergism between the action of magnesium salt and ether or morphine

(Gwathmey [59] and others); that the solution of magnesium sulphate paralyses the exposed motor and sensory nerves (Meltzer and Auer,[58] Liljestrand,[60] and Guthrie and Ryan [61]); that the chief danger of parenteral administration of magnesium sulphate consists primarily in the paralysis of respiration due in cases of moderate doses mainly to the curare action, and that only much greater quantities can produce cardiac arrest due to well known cardio-inhibitory action of magnesium; that magnesium sulphate can be useful in the symptomatic treatment of tetanus (Kocher [62]; Meltzer [63]) and against strychnine and other convulsants; that after the magnesium sulphate anæsthesia there can appear some diuresis together with cylindruria and glycosuria. Later on the magnesium sulphate was recommended for the treatment of asthmatic crises and of endarteriitis obliterans as well as for certain diagnostic and therapeutic procedures like estimation of circulation time or duodenal drainage (Meltzer and Lyon [64] test).

According to Boyd and Scherf [43] the first effort to use the cardio-inhibitory properties of magnesium for the treatment of heart disturbances is due to Seekles,[65] who administered magnesium chloride intravenously to eliminate arrhythmias depending on the injection of calcium chloride into cows suffering from milk fever or grass staggers. But the real interest in these properties of magnesium was only evoked when Zwillinger [66] recommended in 1935 the intravenous injections of 10 c.c. of a 20 per cent solution of magnesium sulphate for the treatment of paroxysmal tachycardia and ventricular premature beats or ventricular flutter. One year later Rothberger and Zwillinger,[67] in very extensive animal experiments succeeded in preventing or eliminating the ventricular tachycardias caused by barium or by digitalis previously known as irreversible. Rothberger [68] pointed out with insistence that the property of arresting the otherwise irreversible digitalis or strophantine ventricular tachycardias is unique and characteristic for magnesium sulphate, the inhibitory action of which is much more strong upon the ectopic pacemakers than upon the S-A node.

The cardio-inhibitory action of magnesium salts was also studied not long ago by Smith, Winkler, and Hoff.[55] They proved that its chief action on the heart consists in the general depression of conduction, i.e. depression of sino-auricular, auriculo-ventricular, and intra-ventricular conduction, the action upon this latter being, however, not so extreme as to provoke the disorganization of the whole ventricular complex, as in case of potassium. The recommendation of Zwillinger to use magnesium salts in order to prevent ventricular flutter and extrasystoles, on the other hand, has been found to be based on scant physiological evidence because such arrhythmias could be induced or appeared spontaneously in the presence of greatly increased concentration of magnesium in the serum.

The clinical evidence, however, presented in the recent paper of Boyd and Scherf [43] confirms entirely the experience of Zwillinger and of Rothberger and Zwillinger, and seems to indicate the usefulness of intravenous administration of a 20 per cent solution of magnesium sulphate in cases of paroxysmal auricular and ventricular tachycardia.

The results of our study also confirm the views of Zwillinger, Rothberger and Zwillinger, and Boyd and Scherf. We have convinced ourselves that the addition of small quantities (0·5 c.c.) of a 20 per cent solution of magnesium sulphate to the intravenous or intracardiac injection of a lethal dose of mercurial diuretic prevents ventricular fibrillation and death of the animal, although particularly after the second and following injections it does not prevent the development of some disturbances of conduction. This is especially marked when the magnesium sulphate in this small dose is given simultaneously with mercurial diuretic. In this way one is able to inject with relatively small intervals of time (about half an hour) doses as much as 7 to 8 times higher than the dose known as lethal for normal dogs, and no persisting harmful effects are apparent. Even when magnesium sulphate is given after the injection of the mercurial diuretic in a lethal dose, it has analogous effect, because it arrests the heart without the phase of ventricular fibrillation, as we had the opportunity to observe a few times.

There seems to be no direct contradiction between the results of our study and those obtained by Smith, Winkler, and Hoff.[55] Many other drugs which in certain conditions are capable of preventing or alleviating ventricular fibrillation, in excessive doses can produce

ventricular fibrillation in experimental animals (Katz [53]). This refers to quinidine, potassium salts, and even to stimulation by faradic current. Boyd and Scherf [43] also mention this paradoxical double influence of cardio-inhibitory drugs and by it explain the frequent appearance of ventricular extrasystoles after the intravenous injection of magnesium sulphate. It is clear, therefore, why magnesium sulphate did not suppress ventricular fibrillation in Smith, Winkler, and Hoff's experiments when the magnesium content of the serum reached an extraordinarily high level of 36 mg. per 100 c.c., although the inhibitory function of this drug upon the stimulus formation can in other conditions, whether clinical or experimental, be so obvious.

The mechanism of this protective action of magnesium sulphate upon the development of ventricular fibrillation in the course of acute intoxication provoked by the intravenous or intracardiac injection of organic mercurial diuretic is not known. A faint suggestion in respect of this mechanism can be looked for, however, in the fact that the injection of magnesium with the mercurial diuretic is more efficient than when it follows the injection of the mercurial diuretic at even only relatively very small interval of time. Some years ago Salant and Nagler [39] attributed the decreased toxicity of mercurial ion for the isolated heart produced by great doses of calcium, to the diminished permeability of the cell membrane. An analogous action of magnesium is known from the study of the nervous system and was brought to the fore by Moore [69] to explain its analgesic rôle. Possibly, therefore, this property of magnesium together with its inhibitory action are responsible for the protective influence offered by it in cases of acute intoxication by mercurial diuretics. Independently, however, of the exact details of this mechanism magnesium sulphate in pertinent doses and injected simultaneously with the mercurial diuretics, seems according to our study to correspond with our first postulate as mentioned in the introduction of this paper, i.e. to exert a protective action on the heart in the course of an acute intoxication by mercurial diuretics.

On the other hand, magnesium does not only not suppress the diuretic activity of mercurial diuretics, but rather increases the diuretic effect of organic mercurial compounds. A certain diuretic property of this drug was known already to Meltzer and Auer,[58] who noted that after anæsthesia with magnesium sulphate there is some diuresis but not diarrhœa. White,[70] in the new edition of his book, lists also magnesium sulphate among diuretics with no very strong diuretic properties when given alone. It is possible that this diuretic action is due mainly to the presence of the sulphate anion in magnesium sulphate molecula, which anion being rejected by the renal tubule is a powerful osmotic diuretic (Goodman and Gilman [7]). Particularly clear is the diuretic activity of magnesium sulphate when administered together with mercurial diuretics. The senior of the authors many years ago used to inject intramuscularly a mixture of organic mercurial compound with 2 to 3 c.c. of a 20 per cent solution of magnesium sulphate, and observed beautiful diuretic responses. The theoretical reason for use of such a mixture was the Elias' [71] hypothesis that diuretic mercurials are initially excreted in bile, and only when re-absorbed from the digestive tract produce their diuretic action. All drugs, therefore, capable of increasing the secretion of bile as, for instance, decholin or perhaps also magnesium sulphate had to be considered according to this hypothesis as provided with synergistic properties in respect of the mercurial diuretics. An analogous mixture, but with much greater content of magnesium sulphate and with the addition of 1·5 c.c. of a 5 per cent procaine hydrochloride, was used for intramuscular injections by Shelling and Tarr,[72] and Marvin [4] expresses the belief that there can be no question " that this combination is sometimes remarkably efficacious with patients who have shown little or no response to salyrgan." Thus magnesium sulphate fulfils the second of our postulates to the effect that injected simultaneously it increases diuretic properties of mercurial diuretics.

Finally, the intravenous injection of such small quantities of magnesium sulphate (0·5 c.c. of a 20 per cent solution) together with mercurial diuretic seems to be completely safe. Boyd and Scherf [43] employed in their series the injection of a 20 per cent solution in amounts from 10 to 20 c.c., even for cases with coronary sclerosis or myocarditis, and no " untoward effects have been observed." They quote the observations of other authors according to which magnesium salts have been given in concentration from 10 to 30 per cent to patients with coronary sclerosis, angina pectoris, etc., without any alarming reaction. Magnesium sulphate in a concentration as high as 42 per cent, though with the addition of calcium gluconate, has been also used many times for the estimation of circulation time, apparently without ill effects. The same refers to dogs, because Moore and Wingo [74] injected their dogs with large doses of

magnesium chloride, and when the injection was stopped before the occurrence of the respiratory arrest some animals survived without permanent injuries although the blood Mg level reached 20 to 24 mg. per 100 c.c. Schmidt and Greenberg [73] estimate the fatal dose of $MgSO_4.7H_2O$ for a dog with normal serum calcium as between 0·23 and 0·28 per kg. We have injected our dogs of a weight of around 10 kg. with 0·5 c.c. of a 20 per cent solution or 0·1 g. of magnesium sulphate, or 0·01 g. per kg. The therapeutic index (relation between fatal and effective dose) was therefore on the base of these data 25 : 1.

The assumption is justified, therefore, that the doses of magnesium sulphate employed by us are completely safe for dogs and particularly for man, and that magnesium sulphate fulfils the third of our postulates, i.e. it is absolutely safe in the doses recommended. We believe that incorporation of small quantities of magnesium sulphate into the solution of mercurial diuretics should be made in order to prevent fatal reactions resulting from intravenous injection of these drugs: in addition, magnesium sulphate mixes with mercurial diuretics without forming any precipitate.

Summary

The course of acute intoxication produced by the intravenous or intracardiac injections of esidrone was studied on normal dogs with the help of the electrocardiograph. It is concluded in agreement with other authors that mercurial diuretics in certain doses are general depressants for the whole cardiac muscle. The following pattern of intoxication was observed: changes of T waves, intraventricular and auriculo-ventricular conduction disturbances, diminution of frequency of impulse formation in S-A node, ventricular paroxysmal tachycardia, chaotic heart action, ventricular fibrillation, and death.

The addition of small quantities of magnesium sulphate (0·5 c.c. of a 20 per cent solution) prevents ventricular fibrillation and death, even if doses 7 times higher than normal lethal doses are used. Magnesium sulphate, however, does not prevent and even perhaps increases the conduction disturbances resulting from the administration of lethal doses of mercurial diuretics. On the other hand, such amounts of magnesium sulphate increase the diuretic response, are entirely safe, and mix with mercurial diuretics without forming any precipitate.

It is suggested that small quantities of magnesium sulphate be incorporated into the mercurial diuretics in order to prevent fatal reactions resulting sometimes from the intravenous injections of these drugs.

References

Owing to the arrangement of this paper, it has been thought best to make an exception to the usual custom and to leave the references in the form presented by the Author, except that the year where given is put after the author's name.—Editor.

1. Blalock, A., Pilcher, C., and Harrison, T. R. (1929). *Amer. J. Physiol.*, **89,** 589.
2. Corrigan, F. P., and Pines, I. (1943). *Surgery*, **14,** 88.
3. Thomson, W. A. R. (1937). *Quart. J. Med.*, **6,** 321.
4. Marvin, H. M. (1940). *J. Amer. med. Ass.*, **114,** 757.
5. Fishberg, A. M. (1937). *Heart Failure.* H. Kimpton, London.
6. Saxl and Heilig: quoted by Fishberg (17).
7. Goodman, L., and Gilman, A. (1941). *The Pharmacological Basis of Therapeutics.* Macmillan & Co., New York.
8. Jendrassik: quoted by Fishberg (17).
9. Fourneau, E., and Mellville, K. I. (1931). *J. Pharmacol. exper. Therap.*, **41,** 21.
10. Blumenthal, F., and Oppenheim, K.: quoted by Fourneau and Mellville (9).
11. Saxl: quoted by Fishberg (17).
12. Scherf, D., and Boyd, L. J. (1939). *Cardiovascular Diseases.* C. V. Mosby, St. Louis.
13. Petersen, A.: quoted by Degraff and Nadler (19).
14. Tursz: Personal communication.
15. Pines: Unpublished observations.
16. Volhard: quoted by Fishberg (17).
17. Fishberg, A. M. (1939). *Hypertension and Nephritis.* Fourth ed. Lea & Febiger, Philadelphia.
18. Stokes: quoted by Degraff and Nadler (19).
19. Degraff, A. C., and Nadler, J. E. (1942). *J. Amer. med. Ass.*, **119,** 1006.

20. Hines: quoted by Degraff and Nadler (19).
21. Evans and Paxon: quoted by Degraff and Nadler (19).
22. Wexler, J., and Ellis, L. B. (1944). *Amer. Heart J.*, **27,** 86.
23. Fox, Th., Gold, H., and Leon, J. (1942). *J. Amer. med. Ass.*, **119,** 1497.
24. Higgins, W. H. (1942). *Ibid.*, **119,** 1182.
25. Wilson: quoted by Degraff and Nadler (19).
26. Parent: quoted by Degraff and Nadler (19).
27. Barker, M. H., Lindberg, H. A., and Thomas, M. E. (1942). *J. Amer. med. Ass.*, **119,** 1001.
28. Friedfeld, L., Kissin, M., Modell, W., and Sussman, R. (1941). *Ibid.*, **117,** 1806.
29. Redlich: quoted by Degraff and Nadler (19).
30. Levin: quoted by Carrillo (45).
31. Dresser: quoted by Rossello, H. J. (1940). *Terapeutica Glinica y Farmacodynamica.* Uteha, Argentina, Buenos Aires.
32. Levine, S. A. (1940). *Clinical Heart Disease.* Second ed. W. B. Saunders, Philadelphia and London.
33. Goodman, J. I., and Corsaro, J. F. (1943). *Amer. Heart J.*, **26,** 338.
34. Mueller, Shoeller, and Schrauth: quoted by Fourneau and Mellville (9).
35. Salant and Kleitman: quoted by Wexler and Ellis (22).
36. Hatcher and Weiss: quoted by T. Sollmann (75).
37. Jackson: quoted by Wexler and Ellis (22).
38. McCrea and Meek: quoted by Sollmann (75).
39. Salant, W., and Nagler, H. (1931). *J. Pharmacol. exper. Therap.*, **41,** 407.
40. Chastain and Mackie: quoted by Barker, Lindberg, and Thomas (27).
41. Johnston: quoted by Degraff and Lehman (19).
42. Degraff, A. C., and Lehman, R. A. (1942). *J. Amer. med. Ass.*, **119,** 998.
43. Boyd, L. J., and Scherf, D. (1943). *Amer. J. med. Sci.*, **206,** 43.
44. Pines, I. (1938). *Wien. Arch. inn. Med.*, **32,** 129.
45. Carrillo, E. G. (1943). *Rev. Med. Costa Rica*, **5,** 425.
46. Samojloff, A. (1910). *Pflueger's Arch. ges. Physiol.*, **135,** 417.
47. Rothberger, C. J., and Winterberg, H. (1910). *Ibid.*, **135,** 506.
48. Kobacker and Rigler: quoted by I. Pines (44).
49. Ruttger: quoted by I. Pines (44).
50. Steinfeldt: quoted by I. Pines (44).
51. Rothberger: quoted by I. Pines (44).
52. Pines, I. (1934). *Arch. Internat. Pharmacodyn. Therap.*, **49,** 91.
53. Katz, L. N. (1941). *Electrocardiography.* Lea & Febiger, Philadelphia.
54. Harrison, T. R. (1935). *Failure of the Circulation.* Willians & Wilkins, Baltimore.
55. Smith, P. K., Winkler, A. W., and Hoff, H. E. (1939). *Amer. J. Physiol.*, **126,** 720.
56. Hay: quoted by Smith, Winkler, and Hoff (55).
57. Matthews and Jackson: quoted by Smith, Winkler, and Hoff (55).
58. Meltzer and Auer: quoted by Sollmann (75).
59. Gwathmey: quoted by Sollmann (75).
60. Liljestrand: quoted by Sollmann (75).
61. Guthrie and Ryan: quoted by Sollmann (75).
62. Kocher: quoted by Sollmann (75).
63. Meltzer: quoted by Sollmann (75).
64. Meltzer and Lyon: quoted by Sollmann (75).
65. Seekles: quoted by Boyd and Scherf (12).
66. Zwillinger (1937): quoted by Endelman and Pines. *O Czestoskurczu napadowyn czasie ciazy porodu.* Warsz. Czas. Lek.
67. Rothberger and Zwillinger: quoted by Endelman and Pines (see 66).
68. Rothberger, C. J.: Personal communication.
69. Moore, R. M. (1934–5). *Amer. J. Physiol.*, **110,** 191.
70. White, P. D. (1944). *Heart Disease.* Third ed. Macmillan & Co., New York.
71. Elias: Personal communication.
72. Shelling and Tarr: quoted by Marvin (4).
73. Schmidt, C. L. A., and Greenberg, D. M. (1935). *Physiol. Rev.*, **15,** 297.
74. Moore, R. M., and Wingo, W. J. (1941). *Amer. J. Physiol.*, **133,** 391.
75. Sollmann, T. (1943). *A Manual of Pharmacology and its applications to Therapeutics and Toxicology.* Sixth ed. W. B. Saunders, Philadelphia and London.

CLINICAL EVALUATION OF THE PRESSOR ACTIVITY OF METHEDRINE, NEO-SYNEPHRINE, PAREDRINE, AND PHOLEDRINE

BY

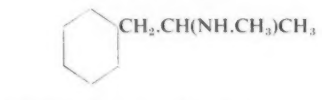
FREDERICK PRESCOTT

From the Wellcome Research Institution, London

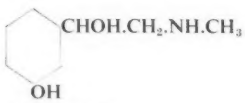
Received October 10, 1944

Recently a number of pressor drugs of the adrenaline type have come into clinical use for the treatment of low blood pressure following surgical procedures, spinal anæsthesia, circulatory collapse, and surgical and traumatic shock. For therapeutic purposes the ideal pressor drug should be effective by the intramuscular or intravenous route; it should act rapidly; it should produce a sustained elevation of blood pressure, so that frequent injections of the drug are not necessary; and it should have no undesirable effects on the cardiovascular system and no untoward side effects. Adrenaline and ephedrine were the first drugs to be used clinically to raise the blood pressure in cases of operative shock. Their limitations, however, are now well known. Adrenaline may do more harm than good because in therapeutic doses intravenously it causes a considerable rise of blood pressure, e.g. 200 mm. to 300 mm. of mercury, with a precipitous fall after a few minutes to a level lower than before. Similarly ephedrine, which for dependable results must be given intravenously, produces a sharp rise of blood pressure that lasts only for ten to twenty minutes. Other pressor drugs have been introduced with a more sustained action. In most of the studies reported on these, however, no definite criteria seem to have been employed in their evaluation, nor have the conditions of administration been standardized. In general the drugs have been given to patients showing a fall of blood pressure after spinal anæsthesia or during surgical operations, but few comparative studies have been made on them.

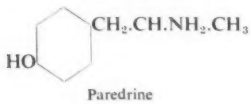
In this investigation an attempt has been made to evaluate in similar conditions the pressor activity of the sympatho-mimetic drugs methedrine (*d*-desoxyephedrine, pervitin), neo-synephrine, paredrine, and pholedrine (paredrinol, veritol). Their chemical relationship to adrenaline and ephedrine is shown in the following formulæ:



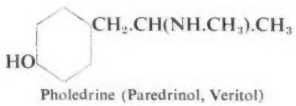
Methedrine (Desoxyephedrine, Pervitin)



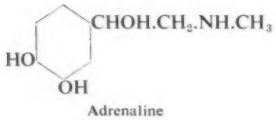
Neo-synephrine



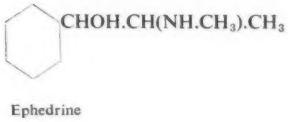
Paredrine



Pholedrine (Paredrinol, Veritol)



Adrenaline



Ephedrine

A detailed study of the pressor effects of methedrine has already appeared (Dodd and Prescott, 1943*a* and 1943*b*). The results of twenty of the cases studied are given in this paper, only those showing a severe fall in blood pressure (average 64/50 mm.) being included.

A number of studies on neo-synephrine have been published (Johnson, 1937; Lorhan and Oliverio, 1938; Bittrich, 1939; Brunner and de Takats, 1939; Silvers and Leonard, 1940; Lorhan and Lalich, 1940; Difabio, Lawrence, and Ascione, 1941) but no comparative clinical tests have been made using patients with a low blood pressure.

Several investigations have been carried out on the pressor activity of paredrine in normal subjects (Abbott and Henry, 1937; Loman, Rinkel, and Myerson, 1939; Altschule and Iglauer, 1940; Iglauer and Altschule, 1940; Myerson and Loman, 1941). Iglauer and Molle (1943) have reported on the pressor effect of paredrine on subjects suffering from infection, but most of them seemed to have a normal blood pressure and were in no need of a pressor drug. It would seem that the best way to evaluate a pressor drug is to give it to a subject with a low blood pressure and see if this can then be maintained at a normal level.

Nathanson *et al.* (1942) investigated the effect of paredrine in spinal anæsthesia. They recorded that the blood pressure was maintained during the operation in 83 per cent of 114 patients who received the drug. In the author's opinion it is not sufficient to follow the blood pressure during the operation only, say, for half to three-quarters of an hour, as the effect of some drugs does not last longer than this and a fall of blood pressure occurs when the patients are returned to the wards. In evaluating a pressor drug readings must be taken over a period of at least two hours. Altschule and Gilman (1939) also used paredrine to prevent a fall of blood pressure during spinal anæsthesia. Only one case was observed in which a satisfactory rise of blood pressure was recorded for more than two hours.

Pholedrine (veritol) has been used since 1937 on the continent to maintain blood pressure during surgical operations. It has been the subject of favourable reports by Dodd and Merton (1939), Dodd (1940, 1942), and Landau, Logue, and Kopelman (1942). In the author's series it was found that the duration of action of pholedrine was only 35 minutes and that repeated injections of the drug were necessary to maintain the blood pressure when this had fallen to 80 mm. systolic or less. In only four cases out of twenty was the response satisfactory according to the standards laid down by the author. Nathanson and Engelberg (1942) state that paredrine shows a greater and more prolonged pressor activity than pholedrine in the normal subject.

Methods Used

The drugs were administered to patients undergoing major operations who experienced a severe fall in blood pressure. The criterion of this was a fall of systolic blood pressure to 80 mm. or less, or a pulse pressure of 10 mm. or less, that persisted for more than twenty minutes to half an hour. If the systolic or pulse pressure showed signs of spontaneous recovery in this period no pressor drug was given.

Whilst it was difficult to standardize exactly the conditions in which the drugs were given, these were much the same for all the patients. Most of the operations were done under spinal anæsthesia, or under local anæsthesia reinforced with an inhalation anæsthetic or with pentothal; a major operation, usually abdominal, was performed in all cases; and the average age was the same in all groups (about 50). The operations included those on the kidney, bladder, and ureter; cholecystectomy; gastrectomy; gastro-enterostomy; laparotomy; excision of the rectum; prostatectomy; radical mastectomy; hysterectomy; lobectomy; and repair of hernia. In most cases the drug was administered intramuscularly; in a few it was given both intramuscularly and intravenously. The intramuscular route was generally chosen because patients with a low pressure and impending shock often have collapsed veins and valuable time may be lost trying to enter them to give an intravenous injection. An efficient pressor drug should, therefore, act quickly when given intramuscularly.

No injections were given subcutaneously as it is well known that absorption from the subcutaneous tissues is slow in circulatory failure.

Each drug was given to a group of twenty patients undergoing major surgical operations, selected according to the criteria laid down above. The following were evaluated for each drug: optimum dose to produce an adequate pressor response; systolic and diastolic blood pressures before, and maximum and minimum pressures after administration of the drug; rise of systolic and pulse pressure; time for the drug to act; time taken for the systolic blood pressure to return to its pre-operative level; time taken to produce the maximum rise of blood pressure; effect on pulse rate; duration of action; the number of injections needed to sustain the blood pressure; and any untoward effects. Blood pressure and pulse readings were taken every one to two minutes until the maximum rise was recorded and then further readings were made every five minutes for the first hour and every ten minutes for the second hour. When time permitted readings were taken over a period of several hours.

Certain arbitrary standards were adopted. The time taken for the drug to act was measured by the time between the injection and a rise of 10 mm. systolic pressure. Duration of action was measured by the time the systolic pressure kept above 100 mm. The result of an injection was only rated as satisfactory if the systolic pressure kept above 100 mm. for two hours or more and the pulse pressure was not less than 30 mm. during this period. If a period longer than two hours is taken it is difficult to rule out natural recovery after this time in some of the cases, particularly if the fall in blood pressure is due to the administration of a spinal anæsthetic. It was generally found that, if the blood pressure fell during an operation as a result of spinal anæsthesia and surgical trauma, it did so within half an hour to forty minutes of the start of the operation. It is not only spinal anæsthesia that causes a fall in blood pressure but the added effect of surgical trauma (Papper *et al.*, 1943).

Results

The results are summarized in Table I and presented graphically in Fig. 1. Protocols giving the results of each case and submitted with the paper have been omitted owing to lack of space. The results given in Table I are averages calculated from data obtained from the twenty cases studied with each drug. The blood pressure curves in Fig. 1 were obtained by plotting the average blood pressure of twenty cases calculated at five-minute intervals.

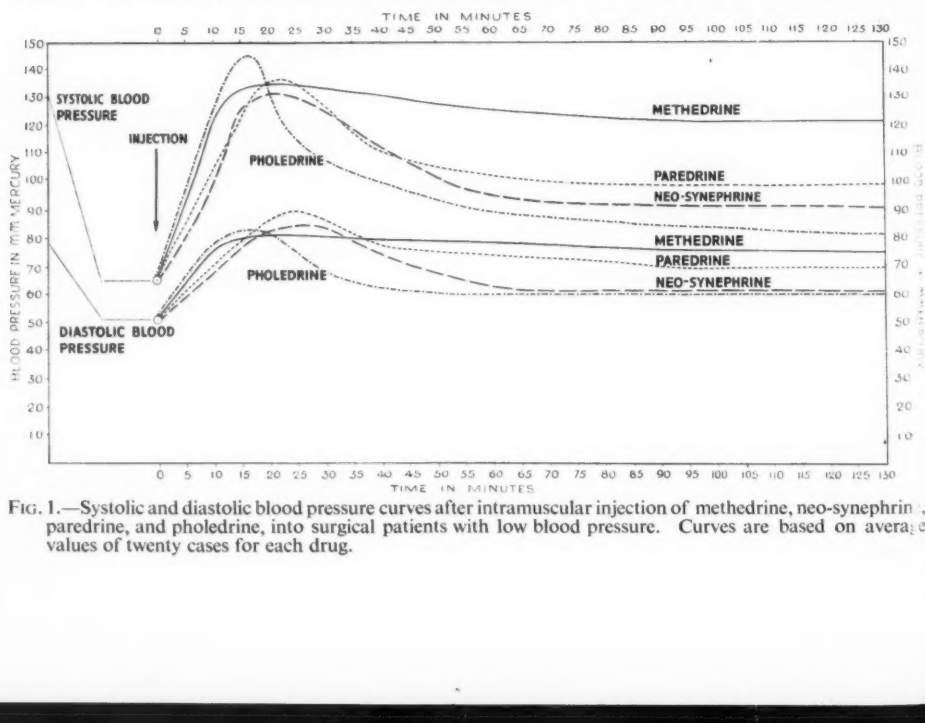


FIG. 1.—Systolic and diastolic blood pressure curves after intramuscular injection of methedrine, neo-synephrine, paredrine, and pholedrine, into surgical patients with low blood pressure. Curves are based on average values of twenty cases for each drug.

TABLE I

EFFECT OF METHEDRINE, NEO-SYNEPHRINE, PAREDRINE, AND PHOLEDRINE ON BLOOD PRESSURE AND PULSE RATE. AVERAGES OF TWENTY CASES

Drug	Dose in mg.	B.P. before operation	B.P. just before giving drug	Max. B.P. after giving drug	Final B.P. after giving drug	Increase or decrease in pulse rate per min.	Time to act (min.)	Time to produce max. rise in B.P. (min.)	Duration of action (min.)
Methedrine	20–30	127/78	64/50	134/80	122/74	+16	3–4	17	Over 120 in 18/20
Neo-synephrine ..	5–7·5	125/75	64/50	132/83	91/62	−11	8	23	42
Paredrine	10–20	132/81	67/53	136/90	99/70	+15	5–6	25	60
Pholedrine	20–30	133/80	73/50	145/84	84/62	+38	4	18	35

Dosage. The actual dose of the drug required to produce an adequate pressor response is not of great importance, unless such a dose is near the toxic level or produces unpleasant side reactions. Many pressor drugs have been evaluated in terms of the minimal dose required to produce a pressor response, the drug which produces the required response in the smallest dose being rated as the most potent. The duration of action, which is important clinically is often overlooked. In this investigation it was found that the following doses were approximately equipressor in activity when given intramuscularly:

Neo-synephrine	5 mg. to 7·5 mg.
Paredrine	10 mg. to 20 mg.
Methedrine	20 mg. to 30 mg.
Pholedrine	20 mg. to 30 mg.

Repeated administration is usually necessary in the case of pholedrine and neo-synephrine to maintain a blood pressure that has fallen. Out of 20 cases repeated injections were needed in 17 patients treated with pholedrine; in 13 treated with neo-synephrine; in 12 treated with paredrine; and in 2 treated with methedrine.

Effect on Systolic Pressure. All four drugs exert an appreciable action on the systolic blood pressure (Fig. 1). The averages for the maximum systolic blood pressure, the final systolic pressure when the last reading was taken, and the final rise in systolic pressure are given below.

	Average maximum systolic blood pressure in mm. Hg	Average final systolic blood pressure in mm. Hg	Average final rise in systolic blood pressure in mm. Hg
Methedrine	134	122	58
Paredrine	136	99	32
Neo-synephrine ..	132	91	27
Pholedrine	145	84	11

It is seen that whereas pholedrine produces the largest immediate rise this is not maintained, the final systolic pressure being only 84 mm. and the final rise in systolic blood pressure only 11 mm. Methedrine produced the highest final systolic pressure and the highest rise in systolic pressure. This was the difference between the systolic pressure just before the drug was injected and the final reading.

Methedrine was the only drug that kept the systolic blood pressure consistently above 100 mm.

Effect on Pulse Pressure. The pulse pressure is the difference between the systolic and diastolic blood pressures, and is a measure of the force with which blood is pumped from the

heart into the blood vessels. In shock or impending shock it is low. The normal pulse pressure is about 40 mm. In this study a pressor drug was rated satisfactory only if it maintained a systolic pressure of 100 mm. or more and a pulse pressure of at least 30 mm. The maximal and final pulse pressures and the immediate and final rise in pulse pressure are given below.

	Average maximum pulse pressure in mm.	Average final pulse pressure in mm.	Average immediate rise in pulse pressure in mm.	Average final rise in pulse pressure in mm.
Methedrine ..	54	48	40	34
Neo-synephrine	49	29	35	15
Paredrine ..	46	29	32	15
Pholedrine ..	61	22	40	1

Methedrine produced the greatest rise in pulse pressure (40 mm.) and within limits this was maintained (34 mm.). With the other drugs the pulse pressure eventually dropped to less than 30 mm. The least satisfactory drug from the point of view of permanently raising the pulse pressure was pholedrine.

Effect on Pulse Rate. Methedrine, pholedrine, and paredrine increase the heart rate; neo-synephrine slows it. The average figures and ranges are given below.

	Effect of pulse rate per minute	
	Average	Range
Methedrine	+16	−10 to +36
Neo-synephrine	−11	−35 to +46
Paredrine	+15	−24 to +48
Pholedrine	+38	−40 to +80

Actually the effect is variable and unpredictable. Methedrine which normally quickens the heart rate may slow it in some patients, and neo-synephrine which normally slows it, may quicken it in some.

Speed of Action. The time taken for the drug to start acting was taken as the time for a rise of 10 mm. systolic blood pressure to occur. The average time taken for the systolic blood pressure to return to its original level and the average time to produce the maximum rise in systolic blood pressure were also noted. The average times are given below.

	Time to act	Time to return B.P. to original level	Time to produce maximum rise in B.P.
	min.	min.	min.
Methedrine	3–4	13 (18/20 cases)	17
Pholedrine	$4\frac{1}{3}$	14 (14/20 cases)	18
Neo-synephrine ..	8	13 (14/20 cases)	23
Paredrine	$5\frac{1}{2}$	17 (11/20 cases)	25

Methedrine and pholedrine appear to act most rapidly, then neo-synephrine, and finally paredrine.

Duration of Action. The drug with the most prolonged action was methedrine. In 18 out of 20 cases the duration of action was over two hours. Only 2 cases were recorded in which the drug failed to maintain the blood pressure above 100 mm. systolic or the pulse pressure at 30 mm. or more for two hours.

Next in order came paredrine. The average duration of action in the 20 cases was 60 minutes. In only 8 out of 20 cases, however, was the effect prolonged for two hours or more.

The duration of action of neo-synephrine averaged 42 minutes in the 20 cases. In 13 of them it averaged 30 minutes. In only 7 cases out of 20 was the effect prolonged for two hours or more.

Pholedrine was the most evanescent of the four drugs in its action. The average duration

of action was 35 minutes. In only 4 cases out of 20 was the effect of the drug prolonged for two hours.

Reactions from the Drugs

The commonest side effect produced by these drugs is a disturbance of cardiac rhythm and the production of systolic heart murmurs. These effects are transient and usually do not last for more than a few hours. In each patient the cardiovascular system was examined clinically before and after giving the drug. The fewest cardiac disturbances were experienced with methedrine and the most with neo-synephrine. The results are summarized below.

	Extrasystoles and other disturbances of rhythm	Apical and pulmonary systolic murmurs	Altered heart sounds
Neo-synephrine ..	5	3	1
Pholedrine	5	2	—
Paredrine	3	4	—
Methedrine	2	1	—

The bradycardia produced by neo-synephrine may result in a pulse rate as low as 30 a minute, according to Brunner and de Takats (1939), who have recorded partial heart block after administering the drug. No untoward effects of this nature were observed with neo-synephrine in this study.

Electrocardiograms were taken in four persons receiving methedrine, but no significant changes were observed. The cardiogram was normal the day after the author received a dose of 70 mg. intramuscularly in divided doses. Unfortunately there were no facilities for taking cardiograms with the other drugs.

Methedrine appears to be the only one of the four pressor drugs with a marked stimulating effect on the cortical centres. This is in the normal person. The effect was not noticed in patients submitted to surgical operations, being presumably neutralized by the premedication with morphine, the anæsthetic, and the post-operative morphine, which was usually given afterwards to patients undergoing major operations.

Summary and Conclusions

The clinical effectiveness of four pressor drugs, methedrine (pervitin, *d*-desoxyephedrine), paredrine, neo-synephrine, and pholedrine (veritol, paredrinol) has been examined. Each drug was tested on twenty patients showing a severe fall in blood pressure (to 80 mm. systolic pressure or to 10 mm. pulse pressure) during major surgical operations. The following were evaluated for each drug: optimum dose for a pressor response; maximum systolic and diastolic blood pressures, and rise in systolic and pulse pressure after giving the drug; effect on pulse rate; time taken for the drug to act; duration of action; and side effects on the cardiovascular system. On the basis of the results obtained the clinical effectiveness of the four pressor drugs examined is in this order: methedrine, paredrine, neo-synephrine, pholedrine. The principal criteria on which this opinion is based are: rise of systolic and pulse pressure when the drugs are given to surgical patients with a systolic blood pressure of 80 mm. or less; the speed and duration of action; and the relative freedom from side effects on the cardiovascular system.

The table below summarizes the results obtained.

	Methedrine	Paredrine	Neo-synephrine	Pholedrine
Satisfactory result	18	8	7	4
Unsatisfactory result	2	12	13	16
	20	20	20	20

A result was rated as satisfactory if the systolic pressure remained above 100 mm. and the pulse pressure was not less than 30 mm. for a period of two hours or more.

Thanks are due to Mr. H. Dodd, Surgeon to the King George Hospital, Ilford, and Mr. Turner Warwick, Surgeon to the Middlesex Hospital, for their assistance and co-operation in this work.

REFERENCES

Abbott, W. O., and Henry, C. M. (1937). *Amer. J. med. Sc.*, **193,** 661.
Altschule, M. D., and Gilman, S. (1939). *New Eng. J. Med.*, **221,** 600.
Altschule, M. D., and Iglauer, A. (1940). *J. Clin. Invest.*, **19,** 497.
Bittrich, N. M. (1939). *Anesth. & Analg.*, **17,** 44.
Brunner, R. S., and de Takats, G. (1939). *Surg. Gynec. Obst.*, **68,** 1021.
Difabio, F. X., Lawrence, J., and Ascione, J. F. (1941). *Anesth. & Analg.*, **20,** 88.
Dodd, H., and Merton, G. (1939). *Brit. J. Surg.*, **27,** 78.
Dodd, H. (1942). *Lancet*, **1,** 498.
—— Prescott, F. (1943*a*). *Brit. med. J.*, **1,** 345.
—— Prescott, F. (1943*b*). *Surg. Gynec. Obst.*, **79,** 645.
Iglauer, A., and Altschule, M. D. (1940). *J. Clin. Invest.*, **19,** 503.
Iglauer, A., and Molle, W. E. (1943). *Amer. Heart J.*, **26,** 247.
Johnson, C. A. (1937). *Surg. Gynec. Obst.*, **65,** 458.
Landau, E., Logue, V., and Kopelman, H. (1942). *Lancet*, **2,** 210.
Loman, J., *et al.* (1939). *Amer. Heart J.*, **18,** 89.
Lorhan, P. H., and Oliverio, R. M. (1938). *Anesth. & Analg.*, **17,** 44.
Lorhan, P. H., and Lalich, J. (1940). *Ibid.*, **19,** 66.
Myerson, A., and Loman, J. (1941). *New Eng. J. Med.*, **224,** 412.
Nathanson, M. H., *et al.* (1942). *Amer. Heart J.*, **24,** 153.
—— Engelberg, H. (1942). *Proc. Soc. Exp. Biol. Med.*, **51,** 239.
Papper, E. M., *et al.* (1943). *J. Amer. med. Ass.*, **121,** 27.
Silvers, H. I., and Leonard, I. E. (1940). *Amer. J. Surg.*, **50,** 79.

THE UNITY OF PAROXYSMAL TACHYCARDIA AND AURICULAR FLUTTER

BY

WILLIAM EVANS

From the Cardiac Department of the London Hospital

Received November 11, 1944

It is difficult in the common electrocardiogram of paroxysmal tachycardia to identify the auricular wave and to place it in relation to the ventricular complex. Accordingly the cardiographic classification for paroxysmal tachycardia based on the position of the P wave (deformed and preceding the R wave in the auricular type, succeeding or coinciding with the R in the auriculo-ventricular or nodal variety, and normal in the ventricular type) has not always been easy to follow in practice. Again, the record has often resembled that customarily called auricular flutter. As a rule the rhythm is readily distinguished from sinus tachycardia. Fortunately the treatment of paroxysmal tachycardia has not suffered from failure to understand its exact mechanism, since attention has usually been directed to the underlying heart condition, and digitalis and quinidine have been given a trial for the correction of the arrhythmia. Nonetheless, the actual mechanism of the attack has engaged the diligent search of many investigators, and a contribution to this subject is worth while.

The clear portrayal of auricular movements in auricular fibrillation (Fig. 1) in the right pectoral (CR_1) cardiogram (Evans, 1941) led me to apply chest leads to patients with paroxysmal tachycardia at the time of the attack. This paper gives the result of such cardiographic examination in 27 consecutive cases. The diagnosis of paroxysmal tachycardia was made when each patient told of periods of palpitation, starting abruptly and usually ending as suddenly after lasting a variable time during which the heart rate was very rapid, and when the limb lead cardiogram showed a high frequency of the ventricular beat, absence of sino-auricular rhythm, and auricular waves removed from their customary place in relation to the ventricular waves if decipherable at all. It is inevitable, therefore, that some of the tracings recorded here might be regarded by some as instances of auricular flutter, although they conform to the definition given above.

During the early part of the investigation three chest leads were used, namely, the right pectoral (CR_1), apical (IVR), and the posterior axillary (CR_7). When it became evident that the auricular waves did not show to better advantage in CR_7 than in the limb leads, it was discontinued as a routine test. Sometimes the auricular movements were depicted clearly in IVR, but they were best in CR_1 so this lead was taken in every patient.

Results of the Investigation

The first tracings showed tachycardia with auricular beats twice as numerous as the ventricular, and when the CR_1 cardiogram was examined for the complete series it showed 2 : 1 A-V dissociation in every patient, although the limb lead had not often indicated this fact. For the purpose of analysis the cases may be separated into three groups according to the auricular and ventricular rates and the relationship of the auricular waves to the QRS

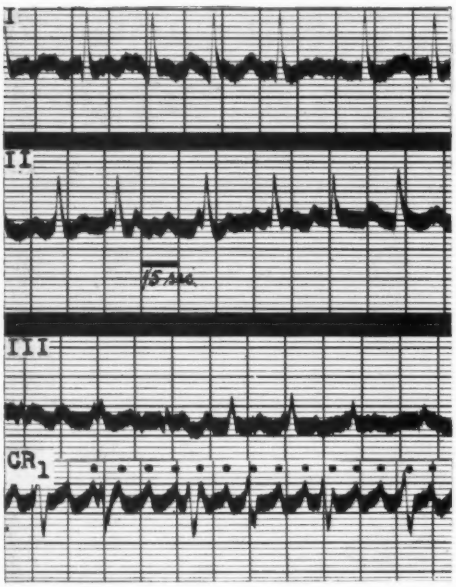


FIG. 1.—Auricular fibrillation; auricular rate (A.R.) 428, ventricular rate (V.R.) 150. Auricular waves in CR_1 show regular rhythm but slight irregularity in form. Male, aged 52, with cardiac infarction. In this and in other figures dots or arrows designate auricular beats.

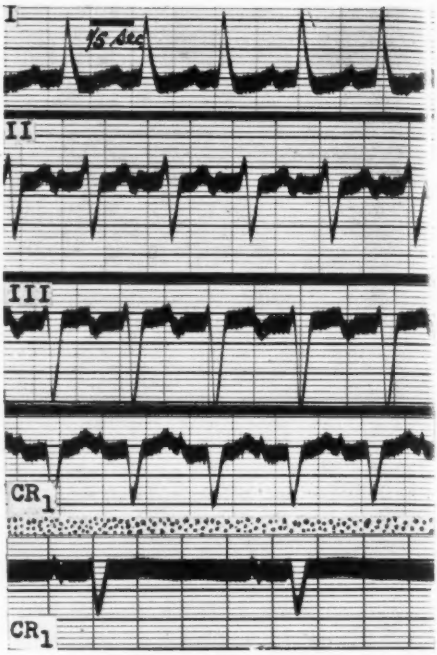


FIG. 2.—Sinus tachycardia resembling auricular tachycardia in limb leads. CR_1 recorded when pulse was rapid and again at normal rate, confirmed sinus rhythm. Flat T wave in second CR_1 from digitalis effect. Healthy female, aged 44, complaining of palpitation.

and T waves in the CR_1 lead. In one group, the rate was slow enough to allow both auricular waves to be shown. In another, the rate was more rapid so that one auricular wave was visible and the alternate one obscured by the coincidence of either the S or T wave of the ventricular complex. In the third group the rate was so rapid as to include and hide both auricular waves in the S and T waves respectively. Naturally the identification of A-V dissociation was not difficult in cases forming the first of these groups from reference to the limb lead cardiogram, but it was impossible in the other two groups. It is known that separation of the auricular and ventricular waves, by slowing the ventricular rate, cannot always be brought about by such measures as digitalization, quinidine therapy, and pressure on the carotid sinus, and in this series also such procedures commonly failed. It was possible, however, to identify the higher frequency of the auricular beats in the CR_1 cardiogram of each of the 27 cases in spite of the handicap of moderately severe tachycardia at times; the identification of the auricular waves in the second and third groups was helped by comparing the right pectoral tracing with one taken during normal rhythm either before or after the paroxysm. The value of this plan is illustrated in cardiograms from a patient thought to have paroxysmal tachycardia; during a spell of palpitation the rapid auricular waves were seen in CR_1 tracing (Fig. 2) to have the same rate as the ventricular waves. If an extra auricular wave had been present in this case it would have coincided with the S wave and produced an R^1 wave in CR_1 during the attack. Since the S wave has the same pattern during tachycardia and when the rate was normal, the rapid heart action arose from the sino-auricular node.

TABLE I

THE RIGHT PECTORAL ELECTROCARDIOGRAM (CR_1) IN 27 CONSECUTIVE CASES OF PAROXYSMAL TACHYCARDIA, AND IN 7 CASUAL EXAMPLES OF ESTABLISHED AURICULAR FLUTTER

Initials or Case No.	Age	Nature of underlying heart disease	Auricular rate		Ventricular rate		Distinctive features of the right pectoral electrocardiogram	Particular ventricular wave obscuring auricular wave
			Individual	Group †	Individual	Group		
F. A.	61	Hypertension	280		23		3 : 1 (or greater)	—
E. C.	62	Hypertension	280		34		A-V dissociation.	—
E. D.	62	Healthy	230		40		Three or more con-	—
A. E.	43	Mitral stenosis	328	Variable	50	Under	secutive auricular	—
P. B.	70	Healthy	292		73	100	waves outside	—
F. S.	57	Hypertension	300		75		ventricular waves	—
H. D.	50	Mitral stenosis	236		80			—
1	46	Mitral stenosis	210		105		2 : 1 A-V dissocia-	—
2	60	Mitral stenosis	212	200	106	100	tion. Both auricular	—
3	21	Healthy	240	to	120	to	waves outside	—
4*	69	Hypertension	254	260	127	130	ventricular waves	—
5*	28	Mitral stenosis	256		128			—
6	68	Hypertension	260		130			S
7*	58	Mitral stenosis	264		132			S
8	65	Mitral stenosis	264		132			S
9	53	Mitral stenosis	282		141			S
10	52	Mitral stenosis	282		141			T
11	63	Hypertension	292		146		2 : 1 A-V dissocia-	S
12	58	Mitral stenosis	300	260	150	130	tion. Alternate	S
13	38	Healthy	308	to	154	to	auricular waves	S
14	34	Healthy	320	400	160	200	within a	S
15*	61	Hypertension	332		166		ventricular wave	T
16*	50	Mitral stenosis	338		169			T
17	64	Healthy	342		171			S
18	53	Cardiac infarction	364		182			S
19*	59	Cardiac infarction	376		188			T
20	19	Healthy	380		190			S
21	50	Healthy	400		200			S and T
22	22	Healthy	400		200		2 : 1 A-V dissocia-	S and T
23*	55	Cardiac infarction	400	Over	200	Over	tion. Both auricular	S and T
24	25	Healthy	422	400	211	200	waves within	S and T
25	54	Mitral stenosis	434		217		ventricular waves	S and T
26	42	Mitral stenosis	434		217			S and T
27	42	Healthy	496		248			S and T

* Denotes that the patient has since died.

† The arrangement in four groups is based on the auricular rate and the degree of A-V dissociation, both of which determine the conspicuity of the auricular waves in the cardiogram.

Auricular Tachycardia of High Rate

When the ventricular rate was 100 to 130 a minute and the auricular rate 200 to 260, both auricular waves were visible outside the QRS and T waves, so that 2 : 1 A-V dissociation was obvious. Five of the 27 cases belong to this group (Cases 1 to 5; Fig. 3, 4, 5, and 6). The cardiogram in one case (Fig. 3) emphasizes how the clear portrayal of the auricular waves depends on the rate; thus in the CR_1 lead both auricular waves were visible when the auricular rate was 210 a minute, but when the rate was 300, one auricular wave became obscured within the S wave. The tracing from another patient (Fig. 7) similarly shows how the hidden auricular waves at high rate are unmasked when the A-V dissociation changes from 2 : 1 to 3 : 1 or 4 : 1. Three of the five patients had mitral stenosis, one was otherwise healthy and the other had hypertension and heart failure. Two have since died and three survive. Quinidine produced no effect on the arrhythmia in two of the patients in whom it was tried; in another the rhythm changed to auricular fibrillation and later to normal rhythm during quini-

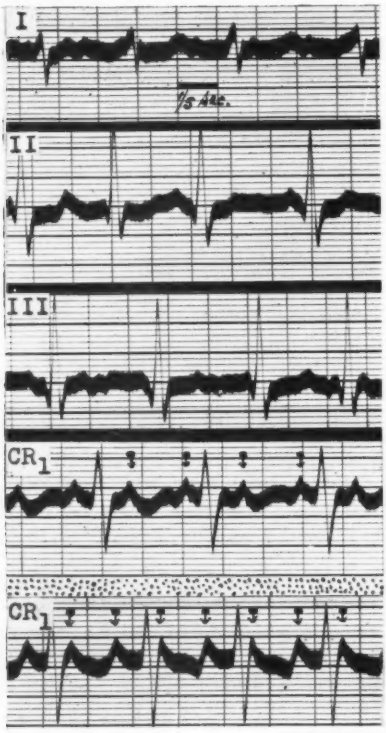


FIG. 3.—Auricular tachycardia with 2 : 1 A-V dissociation; A.R., 210. Both auricular waves outside ventricular waves. Second CR_1 shows a more rapid rate (A.R., 300) so that one auricular wave is now obscured by S wave. Case 1.

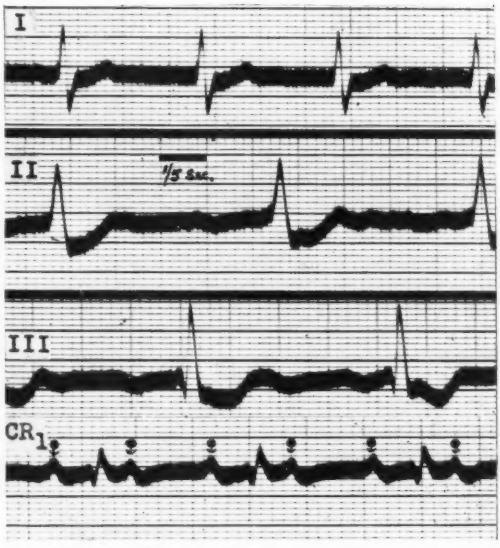


FIG. 4.—Auricular tachycardia with 2 : 1 A-V dissociation; A.R., 212. Both auricular waves outside ventricular waves. Case 2.

dine therapy. In three patients digitalis changed the arrhythmia into auricular fibrillation which persisted in two during continued digitalization; in another, digitalis established normal rhythm directly.

Auricular Tachycardia of Higher Rate

When the ventricular rate was 130 to 200 a minute and the auricular rate was 260 to 400, alternate auricular waves were hidden within the S (in 11 cases) or T waves (in 4 cases) of the ventricular complex, and the 2 : 1 A-V dissociation could not be made out in the limb lead tracing, but it was made apparent in the CR_1 record. Fifteen of the 27 cases belong to this group (Cases 6 to 20; Fig. 7 to 14 and 21). When the auricular wave coincided with the S it produced an upright extension of the S in CR_1 above the isoelectric level to form an R^1 wave, and whenever the same lead was recorded in normal rhythm this extra wave was absent. Manifestly this change is not the outcome of tachycardia alone, but is an expression of the presence of an auricular wave, because in rapid tachycardia of sinus origin (Fig. 2) the R^1 is not present. Six of the patients had mitral stenosis, three had hypertension, two had cardiac infarction, and four were healthy. Four have since died and eleven survive. Quinidine was not tried in 8 patients, but in 6 it had no effect, and in another it produced normal rhythm. Digitalis was not tried in 7 patients, but in 2 it had no effect, and in 6 it changed the rhythm into auricular fibrillation which in 2 reverted to normal rhythm.

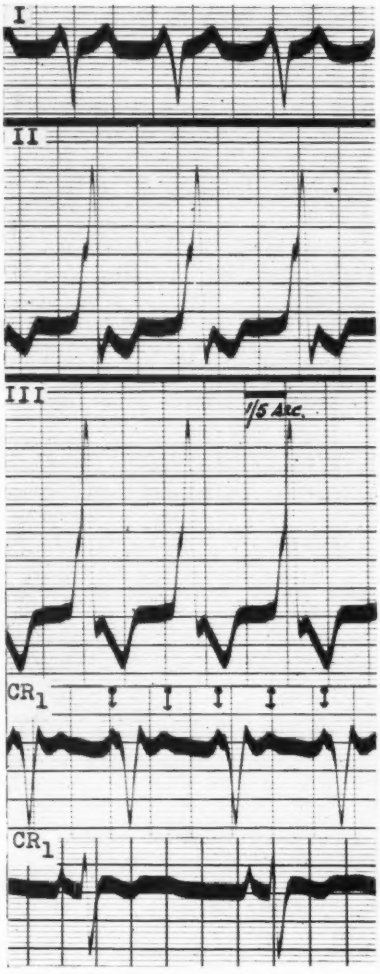


FIG. 5.—Auricular tachycardia with 2 : 1 A-V dissociation ; A.R., 240. Both auricular waves outside ventricular waves. CR_1 in normal rhythm for comparison showing inversion of T wave. Case 3.

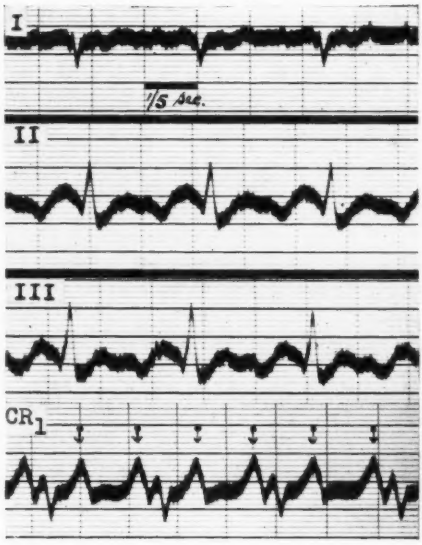


FIG. 6.—Auricular tachycardia with 2 : 1 A-V dissociation; A.R., 256. Both auricular waves outside ventricular waves. Case 5.

Auricular Tachycardia of Very High Rate

When the ventricular rate was over 200 a minute and the auricular rate over 400, both auricular waves were obscured within the S and T waves of the ventricular complex. Even at this high rate the auricular beats were demonstrated by a chest lead cardiogram, and best in CR_1. Seven of the 27 cases belong to this group (Cases 21 to 27; Fig. 15 and 16). Two patients had mitral stenosis; another had cardiac infarction and died when the attack was three days old; four were otherwise healthy. Quinidine was not given to two patients, but in four it failed either to prevent or relieve the attacks; in another it succeeded. Digitalis also had no effect when tried in three of these patients, but it stopped the attack in one other.

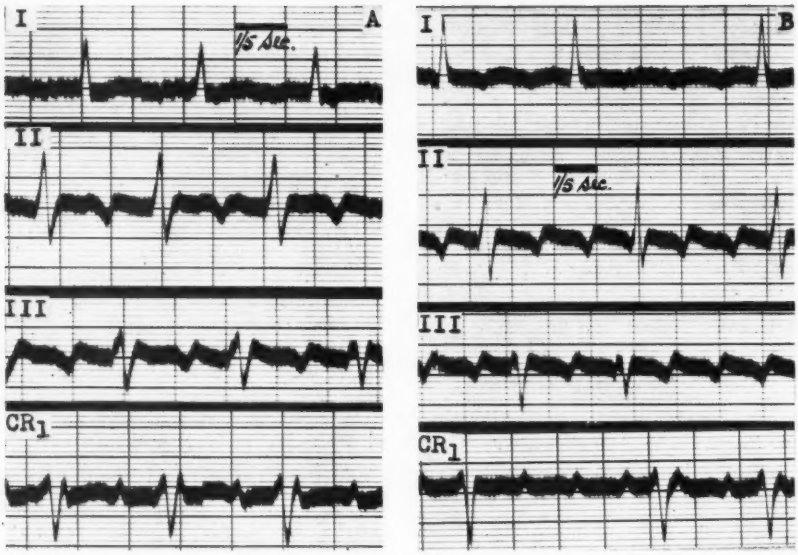


FIG. 7.—Auricular tachycardia with A-V dissociation. In (A) there is 2 : 1 dissociation and A.R. is 260, alternate auricular waves within S. Appearance of tracing suggests flutter. In (B) A.R. is still 260, but A-V dissociation is 3 : 1 and 4 : 1 as a result of reduction in ventricular rate by digitalization. Tracings emphasize effect of ratio of A-V dissociation in obscuring auricular waves in addition to effect of rate. Case 6.

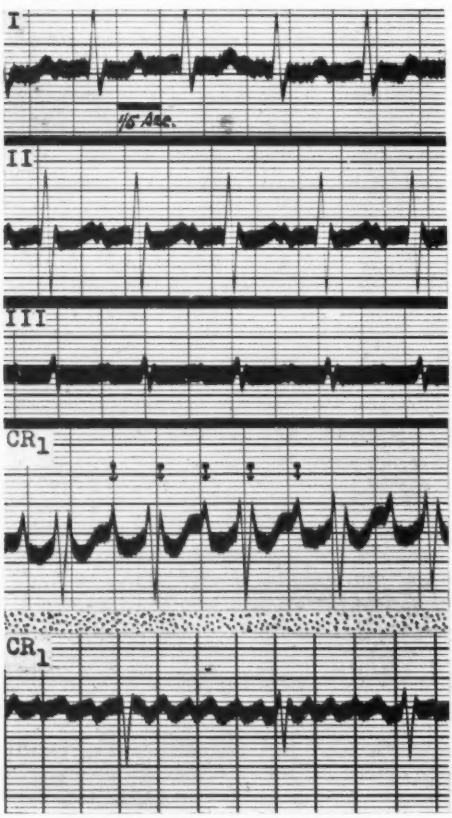


FIG. 8.—Auricular tachycardia with 2 : 1 A-V dissociation; A.R., 264. Alternate auricular waves within S wave producing an R^1 wave. CR_1 in auricular fibrillation for comparison showing disappearance of R^1. Case 7.

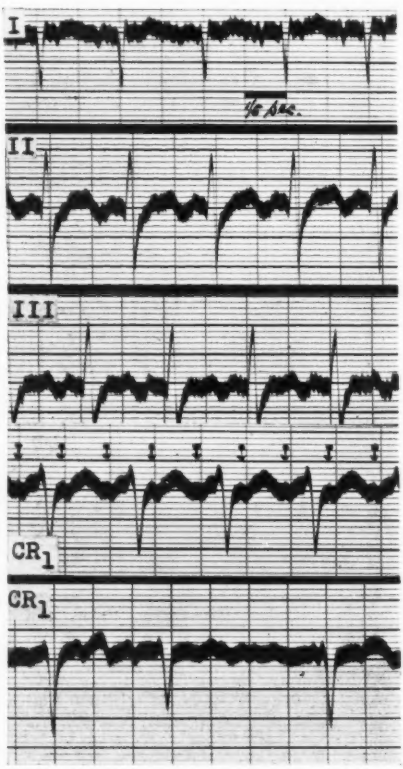


FIG. 9.—Auricular tachycardia with 2 : 1 A-V dissociation; A.R., 300. Alternate auricular waves within S wave. CR_1 in auricular fibrillation for comparison. Case 12.

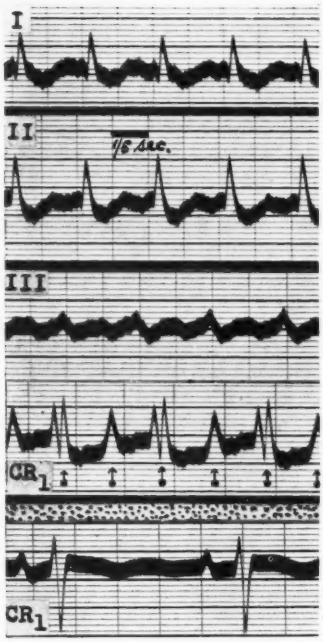


FIG. 10.—Auricular tachycardia with 2 : 1 A-V dissociation; A.R., 264. Alternate auricular waves within S wave producing an R^1 wave in CR_1. CR_1 in normal rhythm for comparison showing disappearance of R^1 wave. Case 8.

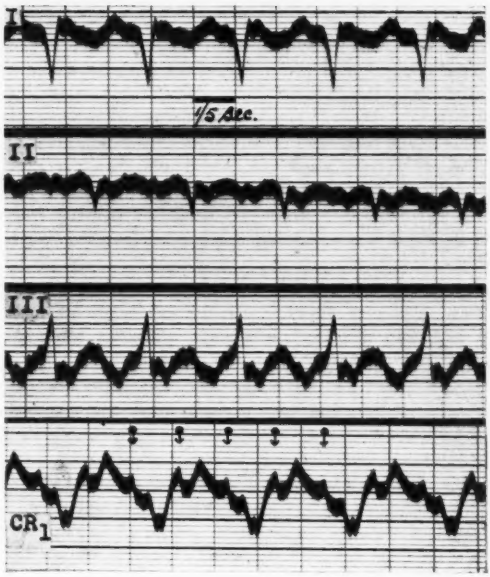


FIG. 11.—Auricular tachycardia with 2 : 1 A-V dissociation; A.R., 282. Alternate auricular waves within S wave producing an R^1 wave in CR_1. Case 9.

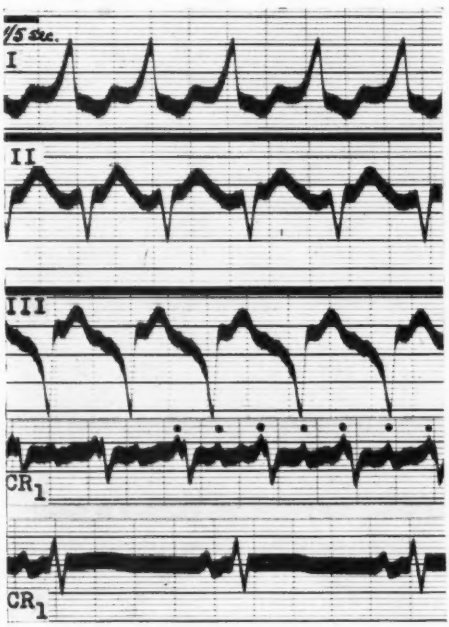


FIG. 12.—Auricular tachycardia with 2 : 1 A-V dissociation; A.R., 282. Alternate auricular waves within T wave. CR_1 in normal rhythm for comparison. Case 10.

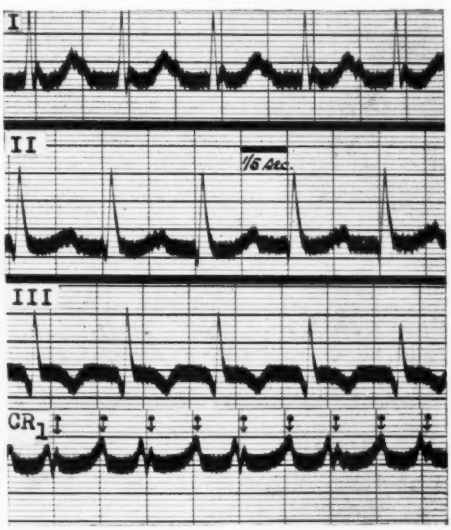


FIG. 13.—Auricular tachycardia with 2 : 1 A-V dissociation; A.R., 308. Alternate auricular waves within S wave producing an R^1 wave in CR_1. Case 13.

FIG. 14.—Short paroxysms of auricular tachycardia in each lead showing 2 : 1 A-V dissociation during such periods when auricular rate was 320. An R^1 and a tall and peaky T wave in CR_1 produced by auricular waves, have disappeared during normal rhythm. Case 14.

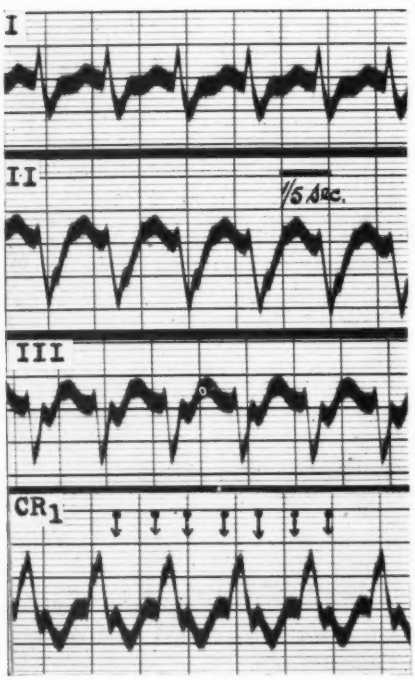


FIG. 15.—Auricular tachycardia with 2 : 1 A-V dissociation; A.R., 400. Auricular waves within S and T waves. Case 22.

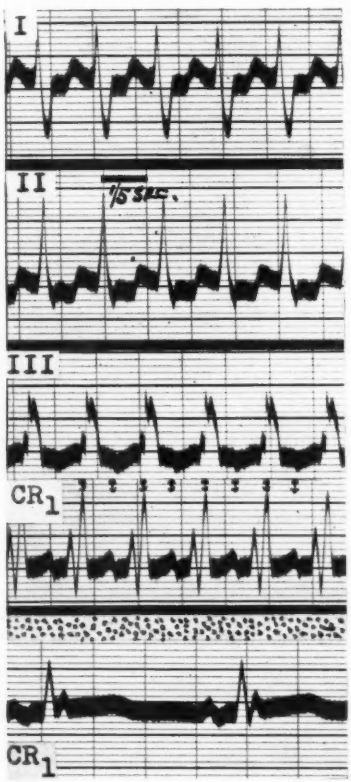


FIG. 16.—Auricular tachycardia with 2 : 1 A-V dissociation; A.R., 496. Auricular waves within S and T waves. CR_1 in normal rhythm for comparison. Case 27.

Auricular Tachycardia with Slow Ventricular Rate

For comparison with the series of 27 cases of paroxysmal tachycardia, I have collected cases that had cardiograms showing a rapid and regular auricular action as an established arrhythmia but with a much slower ventricular rate (under 100 a minute). From among these, 7 have been listed in Table I as being representative of a larger group. The auricular rate varied from 230 to 330 a minute and A-V dissociation was present. The ventricular rate varied from 20 to 100, and at least three consecutive auricular waves appeared outside the ventricular complexes. Rarely, the ventricular beats were regular and very slow because of complete heart block (Fig. 17). In other cases the ventricular beats were more frequent (Fig. 18 and 19) and occasionally occurring irregularly (Fig. 20). The auricular waves in II and III of the limb lead cardiogram from patients in this group conformed to the type customarily regarded as auricular flutter, and the intervals between the auricular waves in CR_1 were at the isoelectric level.

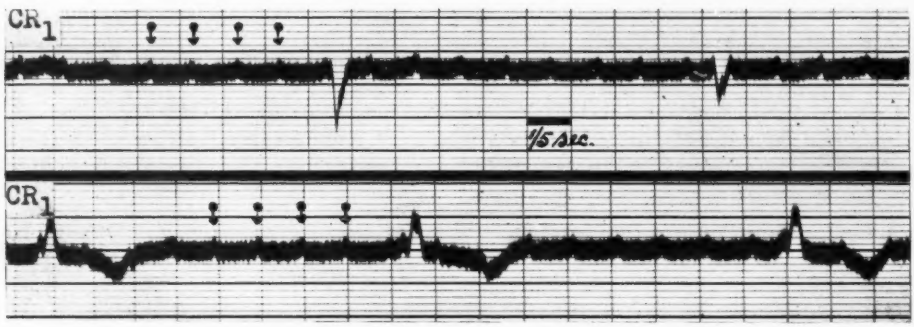


FIG. 17.—Auricular tachycardia with complete A-V dissociation; A.R., 280; V.R., 23. Several consecutive auricular waves appear outside ventricular complexes which in first CR_1 are of right, and in second CR_1 of left bundle branch block type. Female, aged 62, with hypertension.

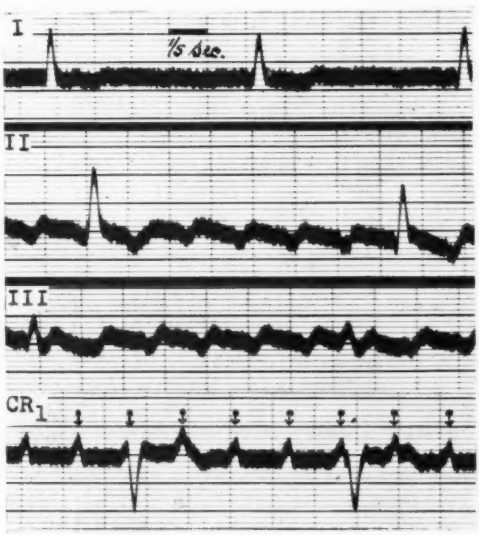


FIG. 18.—Auricular tachycardia with A-V dissociation; A.R., 230; V.R., 40. Three or more consecutive auricular waves outside ventricular waves. Interauricular periods isoelectric in CR_1. Male, aged 62, without heart disease.

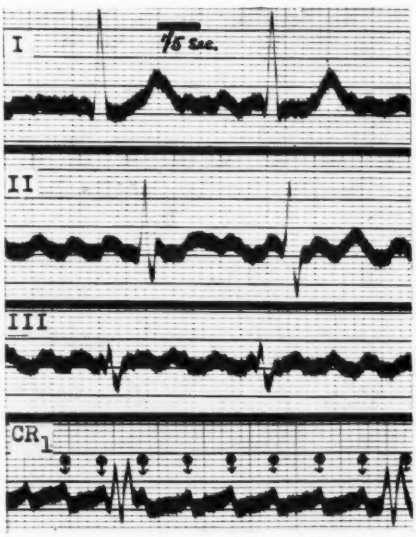


FIG. 19.—Auricular tachycardia with A-V dissociation; A.R., 328; V.R., 50. Three or more consecutive auricular waves outside ventricular waves. Male, aged 43, with mitral stenosis.

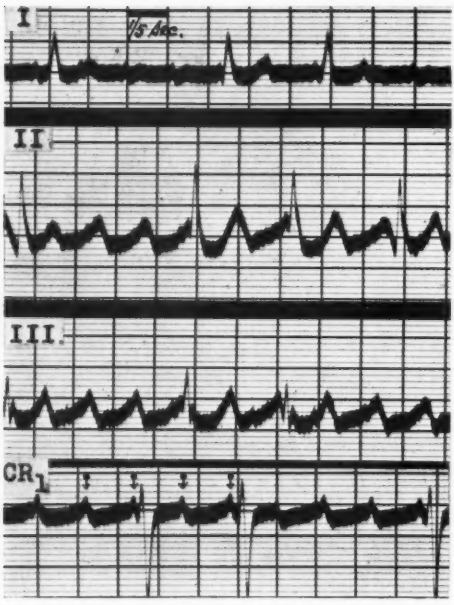


FIG. 20.—Auricular tachycardia with A-V dissociation; A.R., 236; V.R., 80. Three or more consecutive auricular waves outside ventricular waves. Male, aged 50, with mitral stenosis.

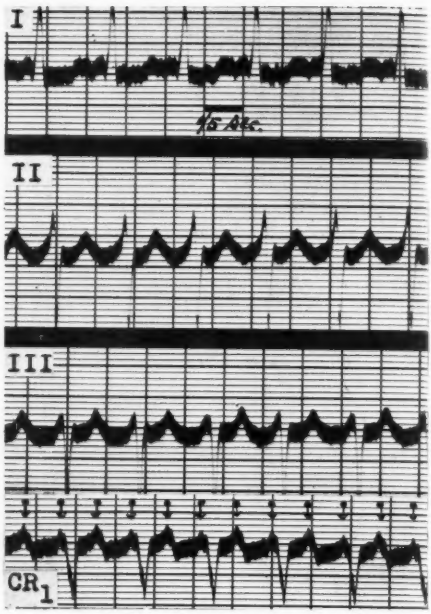


FIG. 21.—Auricular tachycardia with 2 : 1 A-V dissociation; A.R., 338. Alternate auricular waves within T wave. Case 16.

A-V Dissociation in Paroxysmal Tachycardia

Many instances of heart block have been reported in cases with paroxysmal tachycardia. Lewis (1910*a*) found that paroxysmal tachycardia frequently followed the ligation of a coronary artery in the experimental animal; it developed spontaneously whenever there was great acceleration of the ventricular rate. In 12 such instances heart block was noticed, but the auricular rate was half that of the fast ventricular rate. Later Lewis (1910*b*), recording simultaneous curves from auricle and ventricle by myocardiographic levers, alongside an electrocardiogram, demonstrated 2:1 A-V dissociation at high rates. In another paper Lewis (1912) described seven such cases in man; in four of them the auricular and ventricular rates were 300 and 150, 320 and 160, 224 and 112, and 334 and 167, respectively. In the first case the true interpretation of the cardiogram during tachycardia became possible by comparing it with later tracings recorded when the ventricular rate had been halved by digitalis therapy. The cardiogram of another case was shown in a paper by Mackenzie (1910) (his Fig. 56) as an example of paroxysmal tachycardia, but without reference to the 2 : 1 A-V dissociation which it demonstrated. Sprague and White (1925) said that the essential feature of auricular paroxysmal tachycardia, was that the auricles beat regularly and rapidly at a constant rate under the control of an abnormal pacemaker, and that the ventricles maintained an equally rapid rate, contracting in response to all the stimuli; there was no block between the chambers. They found, however, among 56 cases of paroxysmal tachycardia where electrocardiograms were recorded during attacks, 3 instances which were unusual in that they showed heart block. The auricular and ventricular rates in the three cases were 240 and 120, 220 and 110, and 190 and 95, respectively. Single instances of heart block in paroxysmal tachycardia have been reported by Dock (1928), Laubry and Deglaude (1932), Carr (1932), Géraudel (1937), Maddox (1937), Fine and Miller (1940), Tanney and Lilienfeld (1942), and by Parsons (1943).

An important contribution to the incidence of heart block in paroxysmal tachycardia was made by Brown (1936), who recorded an œsophageal electrogram, at the level of the left auricle, in two patients during the attack. Both showed 2 : 1 A-V dissociation. Brown said that his two cases provided evidence that A-V block does occur in auricular paroxysmal tachycardia, and that the auricular rate in this condition may rise certainly to 300 and very probably as high as 428 beats a minute. Barker, Wilson, Johnson, and Wishart (1943) reviewed 17 previously reported cases of auricular paroxysmal tachycardia associated with heart block, and described 18 cases of their own; 6 of their published cardiograms would be regarded by some as auricular flutter. They mentioned that in such cases the attacks often lasted longer than in the common type although they reported notable exceptions. The auricular rate was usually between 165 and 200 a minute, but much higher rates were also met with. They also noticed that patients of this group were often resistant to treatment. Speaking of cardiographic diagnosis they emphasized the difficulty of identifying the nature of the arrhythmia when the P waves were small or indistinct in the standard limb lead cardiogram. In such circumstances they mentioned that chest leads might prove helpful and they used it in 6 of their cases. A notable addition to the number of recorded cases of paroxysmal tachycardia with A-V block has been made by Decherd, Herrmann, and Schwab (1943), who described 40 patients showing this combined arrhythmia. It is not known whether some of their cases showed tracings that might be regarded as typifying auricular flutter because they did not publish the three limb leads in any. Their experience led them to believe that the incidence of A-V block in paroxysmal tachycardia was much commoner than hitherto suspected. Death occurred in 22 cases (55 per cent) during their stay in hospital, and they concluded that the prognosis was serious in this group of patients; only 2 cases in the series were without heart disease, while 35 showed congestive heart failure even before the appearance of the arrhythmia. Decherd and his colleagues believed that the high incidence of heart disease and medication with quinidine or digitalis had contributed to the incidence of A-V block in their patients. The grade of block varied, but 2 : 1 was commonest and was recorded in 21 patients; it was 4 : 3 or 3 : 2 in 18 cardiograms which included three chest records.

The Relationship between Auricular Tachycardia and Auricular Flutter

During paroxysmal tachycardia it is not possible on clinical grounds to tell whether the arrhythmia takes the form of auricular tachycardia or auricular flutter, although auricular flutter is favoured if the attack is prolonged. The difficulty of cardiographic interpretation when the rate is rapid is real. If A-V dissociation became common to auricular tachycardia as well as to flutter, the pertinent question as to the difference between them would need an answer. The inclusion by Barker and his colleagues (1943) of 6 cardiograms that might be regarded by many as examples of auricular flutter, in a paper on paroxysmal tachycardia, provides another reason for examining the subject. Again, in their discussion of a paper on A-V dissociation in 40 cases of paroxysmal tachycardia Decherd *et al.* (1943) say that it must be explicitly stated that we do not possess absolute criteria for sharp differentiation between auricular tachycardia and flutter. Thus, the identification marks customarily applied to each in the past require to be examined again, and decision taken on their specificity for one type or their common application to both. The several characteristics of the two forms of arrhythmia will now be examined.

Historical. The term flutter was first used by MacWilliam (1887) when he wrote about the fibrillar contraction of the heart in the experimental animal. He stated that the phenomena resulting from faradic stimulation of the auricles differed in many respects from those witnessed in the ventricles. The application of the current set the auricles into a rapid flutter, the rapidity of which depended largely on the excitability of the auricular tissue and the strength of the current employed. He described the movements as regular and consisting of a series of

contractions originating in the stimulated area and thence spreading over the rest of the tissue. The movement showed no sign of incoordination, and it looked like a rapid series of contraction waves spreading over the auricular walls. MacWilliam did not tell of the ventricular response to such movements, neither did he record them instrumentally, but only interpreted his visual impression. When Jolly and Ritchie (1910) reported a case of rapid and regular action of the auricle (250 to 300 a minute) they applied the term auricular flutter to the electrocardiogram because it seemed to represent the phenomenon observed and described by MacWilliam during experimental auricular tachycardia. After that the term came into common use.

Duration of the Attack. Auricular flutter, although not uncommonly presenting as brief paroxysms, is more often met with as an established condition. Parkinson and Bedford (1927) stated that flutter in paroxysms constituted a special variety of paroxysmal tachycardia. In about 25 per cent of cases, flutter was purely paroxysmal and was then frequently associated with paroxysms of fibrillation. Auricular tachycardia, on the other hand, although sometimes maintained for long periods, is usually confined to brief attacks. In addition to finding exceptions in each group, I found this distinction between the two kinds of arrhythmia to be fairly closely related to the rate. Thus, cases that show the relatively longer paroxysms of tachycardia have a less rapid auricular rate (300 or less a minute) and often a ratio of A-V dissociation greater than 2 : 1.

The Auricular Rate. A high auricular rate (about 300 a minute) has been regarded as characteristic of auricular flutter, serving to distinguish it from auricular paroxysmal tachycardia with its slower rate of about 160 to 240 a minute. But now that A-V dissociation has been shown to occur in auricular tachycardia, and to be an invariable feature of it in the cases reported here, the high auricular rate may prove to be common to both arrhythmia, at least in most cases. Further, the auricular rate in auricular tachycardia is quite stable as in flutter and is not often altered appreciably by rest, posture, emotion, or exercise.

Response to Treatment. Pressure on the carotid sinus in patients in this series never had the effect of slowing either auricular or ventricular rate sufficiently to separate the auricular and ventricular complexes in the cardiogram. Only once did this manœuvre stop an attack, in a patient in whom the paroxysms were very brief. Parkinson and Nicholl (1922) tried quinidine in six cases of paroxysmal tachycardia, in two of which the attacks were prolonged; in none were they satisfied that quinidine had a beneficial effect. Barker, Wilson, and Johnston (1943) stated that quinidine slowed the heart rate in paroxysmal tachycardia as it did the circus movement in flutter. Quinidine was tried in 15 of the 27 cases; in 12 it had no effect; in one it produced auricular fibrillation; in two it restored normal rhythm. In none did quinidine prevent the return of the attacks. The conversion of paroxysmal tachycardia into auricular fibrillation by digitalis has been reported by Lewis (1912), and by Barker, Wilson, Johnston, and Wishart (1943). Digitalis was tried in 16 of my cases; in 6 it had no effect; in 7 it changed the rhythm into auricular fibrillation, and later normal rhythm was resumed in 3 of these; in 3 digitalis restored normal rhythm directly. Such effects are also witnessed in the treatment of auricular flutter with quinidine and digitalis. Quinidine, or quinidine and digitalis alternately, was tried by Parkinson and Bedford (1927) in the treatment of 27 cases of auricular flutter. They found that digitalis removed flutter far more often than did quinidine. Digitalis alone restored normal rhythm in over a third of the cases, and in another third it induced fibrillation. Quinidine converted flutter directly into normal rhythm in about one case in five; it often cut short paroxysms of flutter, though continued small doses did not entirely prevent their recurrence. Where digitalis had left fibrillation, quinidine sometimes converted this into normal rhythm. Bourne (1933) reported a return to normal rhythm in two out of three cases of paroxysmal tachycardia during digitalization. Campbell and Suzman (1934) observed a case of auricular flutter and rheumatic heart disease for six years; while the patient was taking

the same dose of digitalis as had been dispensed over two years, normal rhythm was restored, but only for three months. In another case of auricular flutter without heart disease, Lewis (1937) watched the arrhythmia continue, without impairment of the heart's efficiency for 24 years; digitalization had proved of no avail.

A-V Dissociation. Hitherto A-V dissociation has been regarded as typical of auricular flutter and a rare happening in paroxysmal tachycardia, but this distinction can no longer apply now that it has been found in so many instances of auricular tachycardia; 17 cases by various authors; 16 by Barker *et al.* (1943); 40 by Decherd *et al.* (1943); and in every case in this series of 27.

Presence of Heart Disease. Out of 100 cases of paroxysmal tachycardia reported by Campbell and Elliott (1939) 55 were healthy. Among 52 cases of auricular flutter examined by Parkinson and Bedford (1927) there were only 5 without heart disease. Another 7 such cases were reported by Orgain, Wolff, and White (1936). Among my 27 cases of paroxysmal tachycardia, there were 11 with mitral stenosis, 4 with hypertension, 3 with cardiac infarction, and 9 who were healthy.

Mechanism. When Mines (1913) described circus rhythm he suggested that it might be responsible for some cases of paroxysmal tachycardia. From their observations on the effects of quinidine upon paroxysms, Iliescu and Sebastiani (1923) believed that auricular tachycardia was due to circus contraction. Lewis (1925) pointed out that the total amount of auricular muscle was not sufficiently large to accommodate a circus mechanism at known rates of conduction in auricular muscle and with cycles as long as those which occur in auricular paroxysmal tachycardia. Now that a more rapid auricular rate has been found common in auricular tachycardia, a circus mechanism cannot be excluded on that ground. This problem has been studied again by Barker, Wilson, and Johnston (1943), and they found strong evidence that auricular paroxysmal tachycardia is caused by circus rhythm involving one of the specialized nodes, either the sino-auricular or auriculo-ventricular node.

Interchangeability of Rhythm. It is known (Lewis, 1912; Parkinson and Matthias, 1915; and Carr, 1932) that paroxysmal auricular tachycardia may change spontaneously to auricular flutter or fibrillation, and flutter or fibrillation may change to paroxysmal tachycardia. This suggests that the conditions are related one to another.

Auricular Deflections and Interauricular Period. In every case in this series the auricular wave was upright in the right pectoral lead suggesting that the ectopic impulse had its origin near the sino-auricular node. It has been held that the auricular movements depicted in the cardiogram of auricular flutter are continuous and that the record does not show any pauses at the isoelectric level between the beats. This is usually true for the limb leads II and III, but it is not true for œsophageal and certain chest leads. Thus in cases that showed such continuous auricular waves in leads II and III, there were usually quiescent intervals between auricular waves at the isoelectric level in the CR_1 cardiogram (Fig. 17, 18, and 20). Similar silent pauses were present in all the other examples of auricular tachycardia. The high auricular and ventricular rate in auricular tachycardia has made the cardiographic diagnosis of auricular flutter less frequent, for the ventricular waves have obscured the pattern of the auricular waves in the limb leads. This is well illustrated in a case of paroxysmal auricular tachycardia reported by Parkinson and Matthias (1915). In their Fig. 4 a sudden infrequency of the ventricular beats has unmasked four consecutive auricular beats which appear typical of those customarily regarded as auricular flutter; the auricular rate of 240 a minute continued as in the earlier part of the record. The same unmasking of auricular beats by a slower ventricular rate is illustrated in Fig. 7 of the present paper. Barker, Wilson, and Johnston (1943) have pointed out that complete separation of the auricular deflections by isoelectric periods is consistent with the continuation of activity during circus movement, provided the circus path traverses either the sino-auricular or auriculo-ventricular node. These authors have postulated that such circumstances operate in paroxysmal auricular tachycardia.

Discussion

There has been no lack of research into paroxysmal tachycardia; indeed the medical literature over a period of 30 years records many observations on the behaviour of the human heart during the attack and under the influence of treatment intended to abort the attack. But the outcome of past research has not been to agree on the nature and mechanism of this rapid heart action. The reproduction of a comparable state in the experimental animal has been difficult so that little help has come from that source. Clinically the description of the attacks has been accepted from patients examined in the intervals between the attacks and in the absence of cardiographic observations during a paroxysm of tachycardia. Gradually, the similarity of paroxysmal tachycardia and auricular flutter has been noticed clinically and cardiographically, and since it has now been shown that A-V dissociation is a common feature of paroxysmal tachycardia as well as of flutter, the common design of the two forms of arrhythmia appears more real. Should this uniformity receive emphasis by the results of further investigation, it will simplify the clinical and cardiographic diagnosis, and allow attention to be directed to a trial of digitalis and quinidine for aborting the attack, and otherwise to consider prognosis and additional treatment in relation to the presence and nature of the underlying heart disease.

If the presence of A-V dissociation in paroxysmal tachycardia, found in every patient in this series, is confirmed by future cardiographic investigation, the terms paroxysmal tachycardia and auricular flutter will have become interchangeable.

Thus, *auricular flutter* is paroxysmal tachycardia in which a moderate auricular rate (200 to 260) facilitates the finding of A-V dissociation in the cardiogram, because both auricular waves are separate from the two main waves of the ventricular complex; a greater A-V dissociation from slowing of the ventricular rate shows three or more consecutive auricular waves outside the ventricular complex even at higher auricular rates.

Again, *paroxysmal tachycardia* is auricular flutter where the more rapid auricular rate (260 to 500) prejudices the recognition of the auricular waves hidden within the ventricular complexes and hinders the discovery of a 2 : 1 A-V dissociation. In such circumstance comparison of a right pectoral cardiogram in an attack with one in normal rhythm will help in deciphering the nature of the arrhythmia.

From the clinical standpoint the attacks in the first group are inclined to be longer, more amenable to digitalis influence, and more certain to be associated with heart disease. But to each of these three distinctive features there are common exceptions.

Conclusion

A right pectoral electrocardiogram (CR_1) demonstrated the presence of A-V dissociation, usually 2 : 1, in 27 consecutive cases of paroxysmal tachycardia. Further investigation is necessary before assigning this feature to all or to the majority of such patients.

In the meantime the finding suggests the common unity of paroxysmal tachycardia and auricular flutter, with auricular tachycardia as the essential mechanism of each, showing variations in rate and in the degree of A-V dissociation.

I wish to thank Dr. John Parkinson, Physician to the Cardiac Department, for his helpful criticism of this paper. Mr. William Dicks, Technician to the Department, has collaborated in producing most of the cardiograms.

Abstract of Case Notes

Case 1. A man, aged 47, with mitral stenosis. Complained of shortness of breath and attacks of palpitation. Systolic and mid-diastolic murmurs in mitral area. No clinical evidence of heart failure. Cardioscopy showed moderate enlargement of heart from mitral stenosis, and slight pulmonary congestion. Electrocardiogram (EC.) shown in Fig. 3.

Quinidine failed to prevent or abort attacks. Digitalis converted arrhythmia into auricular fibrillation.

Case 2. A woman, aged 60, with mitral stenosis. Complained of shortness of breath and palpitation. Clinical evidence of mitral stenosis with much cardiac enlargement, and failure. Cardioscopy showed aneurysmal dilatation of left auricle and pulmonary congestion.

When attack of tachycardia persisted (Fig. 4), digitalis converted it into auricular fibrillation. Quinidine was never tried.

Case 3. An otherwise healthy man, aged 21. Complained of palpitation for over three years. Latterly attacks had lasted for some months. No abnormal signs on clinical or cardioscopic examination. EC. shown in Fig. 5.

Digitalis restored normal rhythm in four days. Quinidine was not tried.

Case 4. A man, aged 69, with hypertensive heart failure. Admitted to hospital because of nocturnal breathlessness. Blood pressure 170/110. Triple rhythm from addition of fourth heart sound, and other signs of left ventricular failure. Diffuse chronic bronchiectasis. Developed bronchopneumonia and tachycardia. EC. showed auricular tachycardia with 2 : 1 A-V dissociation; A.R., 254; both auricular waves outside ventricular waves.

Quinidine changed rhythm to auricular fibrillation and to normal rhythm. Further attacks of tachycardia uninfluenced by quinidine or digitalis, and patient died.

Case 5. A woman, aged 28. Attacks of tachycardia and symptoms of heart failure over some years. Presystolic murmur of mitral stenosis. Cardioscopy showed moderate cardiac enlargement, and pulmonary congestion. EC. shown in Fig. 6.

On one occasion arrhythmia converted into auricular fibrillation by digitalis therapy, but later neither digitalis nor quinidine prevented or relieved attacks. Death took place from heart failure and pulmonary infarction.

Case 6. A man, aged 68, with hypertensive heart failure. Increasing breathlessness for five months. Severe nocturnal dyspnœa for three months. Four attacks of palpitation in last ten days; last attack had been persisting for four days. Great cardiac enlargement and pulmonary congestion from hypertension. EC. shown in Fig. 7.

Quinidine for ten days had no effect on abnormal rhythm, but digitalis over same period slowed ventricular rate and established normal rhythm seven days later.

Case 7. A woman, aged 58, with mitral stenosis and hypertension. Dyspnœa for a year and attacks of tachycardia for a month. Blood pressure 220/115. Clinical signs of mitral stenosis. Cardioscopy showed moderate cardiac enlargement, and pulmonary congestion. EC. shown in Fig. 8.

Digitalis on one occasion changed rhythm to auricular fibrillation. Quinidine was never prescribed. Death came suddenly from pulmonary infarction.

Case 8. A woman, aged 65. Attacks of palpitation for 3 years. Systolic and mid-diastolic murmurs of mitral stenosis. Cardioscopy showed moderate enlargement of heart. EC. shown in Fig. 10.

Quinidine restored normal rhythm on one occasion, and digitalis converted it into auricular fibrillation another time.

Case 9. A woman, aged 53. Sudden onset of tachycardia eight days before. Clinical diagnosis obscured by tachycardia, but cardioscopy showed great enlargement of heart from mitral stenosis. EC. shown in Fig. 11.

Quinidine for 7 days had no effect, but digitalis converted it into auricular fibrillation.

Case 10. A man, aged 52. Frequent attacks of palpitation lasting an hour or a day at a time for eight years. Presystolic murmur of mitral stenosis. Cardioscopy showed moderate enlargement of heart, and slight pulmonary congestion. EC. shown in Fig. 12.

Neither quinidine nor digitalis prevented or aborted attacks.

Case 11. A woman, aged 63, with hypertensive heart failure. Symptoms and signs of left ventricular failure for some months with recent onset of attacks of paroxysmal tachycardia. Cardioscopy showed enlargement of left ventricle, and pulmonary congestion. EC. showed auricular tachycardia with 2 : 1 A-V dissociation; A.R., 292; alternate auricular waves within S wave.

Digitalis and quinidine had no effect on attacks.

Case 12. A man, aged 58, with mitral stenosis. Frequent short attacks of palpitation over many months. EC. shown in Fig. 9.

Quinidine was never given. Digitalis on one occasion changed rhythm to auricular fibrillation and thence to normal rhythm.

Case 13. An otherwise healthy woman, aged 38. Brief attacks of palpitation. No abnormal clinical findings in between attacks. EC. shown in Fig. 13.

Neither quinidine nor digitalis prevented or relieved attacks.

Case 14. An otherwise healthy woman, aged 34. Complained of attacks of palpitation, lasting a few minutes or hours, for 18 months. No abnormal signs on clinical examination which included cardioscopy. EC. shown in Fig. 14.

Neither quinidine nor digitalis was tested for relief or prevention of attacks.

Case 15. A woman, aged 61. Recent onset of heart failure from hypertension, and attacks of palpitation. EC. showed auricular tachycardia with 2 : 1 A-V dissociation; A.R., 332 ; alternate auricular waves within T wave.

Patient died soon after admission into hospital and before quinidine or digitalis could be tried.

Case 16. A man, aged 50. Symptoms of heart failure from mitral stenosis and aortic incompetence for one year with recent onset of attacks of palpitation. EC. shown in Fig. 21.

Patient died in hospital before effects of digitalis or quinidine could be observed.

Case 17. An otherwise healthy woman, aged 64. Complained of frequent attacks of tachycardia lasting for hours at a time and over a period of twelve years. No abnormal signs on clinical examination nor on cardioscopy. EC. showed auricular tachycardia with 2 : 1 A-V dissociation; A.R., 342; alternate auricular waves within S wave.

Neither digitalis nor quinidine proved effective as prophylactic measure.

Case 18. A man, aged 53. Recent cardiac infarction with fall of blood pressure to 90/70. Developed rapid heart action, and EC. showed auricular tachycardia with 2 : 1 A-V dissociation; A.R., 364; alternate auricular waves within S wave. Inversion of T in leads II and III during normal rhythm, disappearing in subsequent tracings, was regarded as effect of tachycardia, but inversion of T I persisted as evidence of cardiac infarction.

Quinidine had no effect on tachycardia, but digitalis changed it into auricular fibrillation before converting it into normal rhythm.

Case 19. A man, aged 59, with hypertensive heart failure. Developed cardiac infarction and rapid heart action. EC. showed auricular tachycardia with 2 : 1 A-V dissociation; A.R., 376; alternate auricular waves within T wave.

Patient died before effects of digitalis or quinidine could be tested.

Case 20. An otherwise healthy woman, aged 19. Recurrent attacks of palpitation. No evidence of heart disease on clinical examination nor on cardioscopy. EC. showed auricular tachycardia with 2 : 1 A-V dissociation; A.R., 380; alternate auricular waves within S wave.

Attack aborted before quinidine or digitalis could be tried.

Case 21. An otherwise healthy woman, aged 50. Periodic attacks of palpitation for 16 years. No evidence of cardiovascular disease on clinical examination nor on cardioscopy. EC. showed auricular tachycardia with 2 : 1 A-V dissociation; A.R., 400; both auricular waves obscured by S and T waves.

Digitalis and quinidine ineffective in relieving or preventing attacks.

Case 22. An otherwise healthy man, aged 22. Four attacks of rapid heart action within six years. Attacks more frequent for three months. On clinical examination and cardioscopy no abnormal signs. EC. shown in Fig. 15.

Digitalis appeared to shorten one attack, and quinidine another.

Case 23. A man, aged 55, with tachycardia three weeks after cardiac infarction. EC. showed auricular tachycardia with 2:1 A-V dissociation; A.R., 400; both auricular waves obscured by S and T waves.

Attack persisted until death, 8 days later. Quinidine failed to change rhythm. Digitalis was not tried.

Case 24. An otherwise healthy man, aged 25. Periodic attacks of palpitation. Clinical and radiological examination showed no cardiovascular disease. EC. showed auricular tachycardia with 2 : 1 A-V dissociation; A.R., 422; both auricular waves obscured by S and T waves.

Neither quinidine nor digitalis was tried.

Case 25. A man, aged 54. Periodic attacks of palpitation over 20 years. Clinical and radiological evidence of mitral stenosis and aortic incompetence. EC. during attack showed auricular tachycardia with 2 : 1 A-V dissociation; A.R., 434; both auricular waves obscured by S and T waves.

Neither quinidine nor digitalis proved beneficial in preventing or relieving attacks.

Case 26. A woman, aged 42. Attacks of palpitation for two years. Cardioscopy showed moderate enlargement of heart from mitral stenosis, but there was no evidence of failure. EC. during an attack showed auricular tachycardia; auricular rate was 434 a minute one time and 218 another time, but with 2 : 1 A-V dissociation on both occasions.

Digitalis and quinidine were not tried.

Case 27. An otherwise healthy man, aged 42. Attacks of tachycardia, lasting upwards of 6 hours, for 5 years. Neither clinical nor radiological examination showed any cardiovascular disease. EC. shown in Fig. 16.

Both quinidine and digitalis failed to prevent or relieve attacks.

References

Barker, P. S., Wilson, F. N., Johnston, F. D., and Wishart, S. W. (1943). *Amer. Heart J.*, **25,** 765.
Barker, P. S., Wilson, F. N., and Johnston, F. D. (1943). *Ibid.*, **26,** 435.
Bourne, G. (1933). *Lancet*, **1,** 686.

Brown, W. H. (1936). *Amer. Heart J.*, **12,** 307.
Campbell, M., and Elliott, G. A. (1939). *Brit. Heart J.*, **1,** 123.
Campbell, M., and Suzman, S. S. (1934). *Lancet*, **2,** 923.
Carr, F. B. (1932). *Amer. Heart J.*, **7,** 668.
Decherd, G. M., Herrmann, G. R., and Schwab, E. H. (1943). *Ibid.*, **26,** 446.
Dock, W. (1928). *Arch. intern. Med.*, **41,** 745.
Evans, W. (1941). *Brit. Heart J.*, **3,** 247.
Fine, M. J., and Miller, R. (1940). *Amer. Heart J.*, **20,** 366.
Géraudel, E. (1937). *Arch. Mal. Cœur*, **30,** 796.
Iliescu, C. C., and Sebastiani, A. (1923). *Heart*, **10,** 223.
Jolly, W. A., and Ritchie, W. T. (1910). *Ibid.*, **2,** 177.
Laubry, C., and Deglaude, L. (1932). *Arch. Mal. Cœur*, **25,** 28.
Lewis, T. (1910*a*). *Heart*, **1,** 98.
—— (1910*b*). *Ibid.*, **1,** 306.
—— (1912). *Ibid.*, **3,** 279.
—— (1925). *The Mechanism and Graphic Registration of the Heart Beat*. Third ed., London.
—— (1937). *Brit. med. J.*, **1,** 1248.
Mackenzie, J. (1910). *Heart*, **2,** 273.
MacWilliam, J. A. (1887). *J. Physiol.*, **8,** 296.
Maddox, K. (1937). *Amer. Heart J.*, **14,** 183.
Mines, G. R. (1913). *J. Physiol.*, **46,** 349.
Orgain, E. S., Wolff, L., and White, P. D. (1936). *Arch. intern. Med.*, **57,** 493.
Parkinson, J., and Bedford, D. E. (1927). *Quar. J. Med.*, **21,** 21.
Parkinson, J., and Matthias, H. H. (1915). *Heart*, **6,** 27.
Parkinson, J., and Nicholl, J. W. McK. (1922). *Lancet*, **2,** 1267.
Parsons, C. G. (1943). *Brit. Heart J.*, **5,** 187.
Sprague, H. B., and White, P. D. (1925). *Med. Clin. North Amer.*, **8,** 1855.
Tanney, A. D., and Lilienfeld, A. (1942). *Ann. intern. Med.*, **16,** 616.

CHEST LEADS FOR THE DEMONSTRATION OF AURICULAR ACTIVITY

BY

P. SZEKELY

From the Cardiovascular Department, Newcastle General Hospital, Newcastle on Tyne

Received September 25, 1944

In certain forms of disorder of rhythm, the correct electrocardiographic diagnosis depends to a great extent on the proper demonstration and interpretation of the activity of the auricles. This is especially the case in paroxysmal tachycardia. However, it is often very difficult with the usual leads to identify the auricular wave and to ascertain its relation to the ventricular deflection, because it may be very small and obscured by the QRS complex or the T wave. Attempts have been made, therefore, to devise special leads in order to obtain large auricular deflections. In this respect, the œsophageal lead (Brown, 1936; Deglaude and Laubry, 1939) is undoubtedly the best method at present, but in view of the hardship it imposes on the patient it can only be used in selected cases and certainly not in routine clinical cardiography. The purpose of this paper is to assess the value of special chest leads employed in this department during the last year in a number of cases, which were under the care of Professor Hume, upon the assumption that they would show auricular waves to much better advantage than the routine leads. I first became interested in this problem in 1940 during my visits to the Cardiac Department of the London Hospital. Dr. William Evans showed me how clearly the auricular waves in various arrhythmias were demonstrated in chest leads and called my attention to this method of investigation.

Lewis (1910) was the first to use special chest leads to facilitate the study of auricular waves. He noticed in cases of auricular fibrillation that the auricular oscillations were maximal when the electrodes were placed over the right auricle. He pointed out that the chest leads as used by him were especially helpful in cases with an enlarged right auricle, for in these cases a larger area of the auricular wall was in apposition to the chest wall. Drury and Iliescu (1921) found that coarse auricular oscillations in auricular fibrillation were more continuously present in the chest leads than in the limb leads. They used two chest leads, sternal and antero-posterior, for the demonstration of auricular activity. In the sternal lead, one electrode at the junction of the second right rib with the sternum was paired with another over the seventh right costal cartilage; in the antero-posterior lead, one electrode was placed on the centre of the sternum, and the other on the back at the level of the inferior angle of the scapula, two inches to the right of the vertebral column. Holzman (1937) observed that the largest auricular deflections in the chest leads occurred when the exploring electrode was placed to the right of the sternum. Lian and Pinchenzon (1938) studied the auricular rhythm in the " precordial auricular lead S 5 ": in this lead, one electrode over the manubrium sterni was paired with another in the fifth right intercostal space. Schoenewald (1939) was able to obtain clearer P waves than those in lead II, by leading off from the right border of the sternum, at the level of the third intercostal space, to the right arm. Evans (1941) studied the auricular activity in lead CR_1 in 60 cases of auricular fibrillation, and showed that in many instances the auricular oscillations

were the most conspicuous in this lead. He failed to notice any close relationship between the size of the right auricle and the amplitude of the P waves. Williams and Ellis (1943) used special auricular precordial leads in their study of ventricular tachycardia: they placed the exploring electrode in the third intercostal space at the right sternal border, using first the right arm and then the left leg for the indifferent electrode; they stated that these leads have repeatedly clarified an otherwise doubtful diagnosis. Barker *et al.* (1943) suggested that in cases in which the P waves are small or indistinct in the standard leads, chest leads might prove helpful; in their opinion, by leading from two precordial contacts, one over the upper part of the sternum and the other over the ensiform process, it is usually possible to record large auricular waves.

Method and Material

The method of taking special chest leads was that adopted by Schoenewald (1939), Faulkner (1943), and Williams and Ellis (1943). A circular electrode, 1·8 cm. in diameter, was used as exploring electrode and was placed in the third intercostal space at the right sternal border. The indifferent electrode was placed either on the right arm (to be referred to in this paper as auricular lead R) or on the left leg (auricular lead F). In several instances both leads were recorded. Except in a few cases, in the initial stage of our study, in which auricular lead F was recorded in reversed polarity for the sake of convenience, both auricular leads R and F and lead IV R were obtained in a manner corresponding closely to the recommendations of the Cardiac Society of Great Britain and Ireland and the American Heart Association (1939) i.e. the galvanometer connections were so arranged that relative positivity of the exploring electrode yielded an upward deflection on the finished curve. For the sake of conformity the few tracings originally recorded in reversed polarity and included in the analysis of this study have been reversed photographically. At first, auricular chest leads were recorded only in cases of paroxysmal tachycardia; but later their use was extended to other forms of arrhythmia and also to a number of cases showing sinus rhythm. Though the majority of the tracings showing sinus rhythm were in other respects abnormal and only a few normal cardiograms were available for comparative purposes, it was thought advantageous to include in this paper all available cases showing normal auricular rhythm.

Paroxysmal Tachycardia

Ten cases were studied. In six, the auricular leads were regarded as helpful, in two cases they were of doubtful value, and in two cases they did not facilitate the reading of the tracings. In all six cases regarded as successful, there were clear P waves in at least one of the auricular leads; while the standard leads and lead IV R usually showed less distinct P waves. The cardiograms of these six cases are reproduced in Fig. 1–7. One of the two cases in which the auricular leads were considered to be of doubtful value was very probably ventricular tachycardia at a rate of 212 a minute. The ventricular complex was broad (0·12 sec.), and there was slurring near the base of the R wave in every second complex in the limb leads and in auricular lead F. The other case appeared to be auricular tachycardia at the rate of 180 a minute. The P waves seemed to be obscured by the T waves in all leads, but the configuration of the S–T segment and the T wave in both auricular leads R and F suggested the presence of a P wave much more strongly than did any of the standard leads. The two unsuccessful cases were thought to be auricular tachycardia. The P waves appeared to be obscured by the T waves and they were not identified with certainty in any of the recorded leads.

The cardiograms reproduced in Fig. 1 are those of a man, aged 63 years, who has had attacks of palpitation for the past four years. He was admitted to hospital for observation on July 7, 1943, and during his five weeks' stay he had several attacks which proved to

A B

FIG. 1.—Case 1 (A). Nodal tachycardia at 176 a minute. Distinct P waves can be seen in auricular lead F. In this and subsequent figures dots denote the sites of the P waves in the auricular leads.
(B). Sinus rhythm. Note the large P waves in auricular lead F.

be paroxysms of supraventricular, probably nodal, tachycardia. No underlying structural disease was found in the heart. Fig. 1A shows such an attack at a rate of 176 a minute. There are no visible P waves in lead I. Though there is some suggestion of P waves in leads II and III, and also in IV R, auricular lead F is the lead in which P waves are most distinctly shown. Auricular lead R is similar to lead I and shows no clear P waves. Fig. 1B was taken a few days later after the tachycardia had stopped. It shows sinus rhythm with big P waves in lead II and in auricular lead F.

The cardiograms shown in Fig. 2 are those of a woman, aged 60 years, who had mitral stenosis and paroxysmal tachycardia. The first tracing shows auricular tachycardia at a rate of 166 a minute, with a 1 : 1 response. Auricular lead F appears to be the best lead for the demonstration of auricular activity. The second tracing, taken after digitalization, shows auricular tachycardia at the same rate as in the previous tracing, with a 2 : 1 A-V block. Here again, auricular lead F shows the most conspicuous P waves. Though the curves resemble auricular flutter, I decided eventually on paroxysmal tachycardia for the following reasons. (1) The rate (166 a minute) appeared to favour paroxysmal tachycardia. (2) The patient having been under observation for a long time before the tracings reproduced were taken had had numerous attacks of tachycardia, and in spite of practically continuous digitalization and massive doses of digitalis during some of the attacks, these attacks were apparently never converted into auricular fibrillation. Though clinically the rhythm was irregular at times and we thought it was auricular fibrillation, the available tracings showed distinct P waves at regular intervals with irregular ventricular activity, and unequal P–R intervals. The auricular deflections were separated by periods of electrical quiescence, thus making auricular flutter with variable block unlikely. I thought there were dropped beats or even A-V dissociation in one of the tracings. (3) Barker *et al.* (194)

FIG. 2.—Case 2 (A). Probably auricular tachycardia with 1 : 1 response. Discussed in text. Rate 166 a minute. Clear, upright P waves in auricular lead F.
(B). Probably auricular tachycardia with 2 : 1 A-V block. Discussed in text. Note the large P waves in auricular lead F.

reproduced tracings which they interpreted as auricular tachycardia and some of them appeared very similar to my tracings—Barker's Fig. 2B, on page 773, interpreted as auricular tachycardia with a 1 : 1 response, and Fig. 2C, same page, following digitalis, as auricular tachycardia with 2 : 1 A-V block. Fig. 6A, on page 778, is strikingly similar to my Fig. 2B. Barker's Fig. 13A also shows similar features.

The curve shown in Fig. 3 was obtained from a R.A.F. pilot, aged 20 years, who was admitted to hospital in an attack of tachycardia.* A similar attack six months previously had lasted for three days. The heart was normal in size on radioscopy, and apart from the tachycardia no abnormality could be detected. The cardiogram shows a tachycardia with a ventricular rate of about 160 a minute. The QRS complex is slightly widened but not grossly aberrant. Leads I and III are not suitable for the analysis of auricular activity. Leads II and IV R suggest P waves at a rate lower than that of the ventricles. Clear inverted P waves can be identified in auricular lead F at a rate of 100 a minute, so that the diagnosis of ventricular tachycardia seems to be justified.

The patient whose cardiogram is reproduced in Fig. 4, was a woman, aged 64 years, who had high blood pressure and heart failure. In the first lead the rhythm is irregular and no P waves can be identified, simulating auricular fibrillation. In lead II, the ventricular complexes are slightly irregular in time, the rate varying from 134 to 166 a minute; here, there is definite evidence of regular auricular activity at a rate of about 158 a minute. Lead III is similar to lead I as regards rhythm. In lead IV R the ventricular rhythm is more or less regular, 158 a minute, and auricular waves cannot be identified with certainty. There is no clear evidence of auricular activity in auricular lead R. Auricular lead F shows clear, inverted P waves at slightly irregular intervals, at a rate of about 158 a minute. This is probably a case of paroxysmal tachycardia with auriculor-ventricular dissociation, and with high auricular and ventricular rates.

The cardiogram shown in Fig. 5 is that of a man, aged 62 years, who was admitted to hospital in a desperate condition. The physical examination revealed a regular tachycardia. The patient died a few hours later, and autopsy showed a slight degree of coronary sclerosis,

* For this case I am indebted to Dr. George Davison.

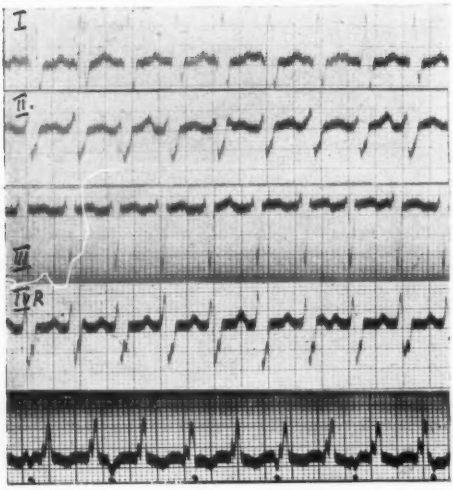


FIG. 3.—Case 3. Ventricular tachycardia. Ventricular rate 160 a minute, auricular rate 100 a minute. Clear, inverted P waves in auricular lead F.

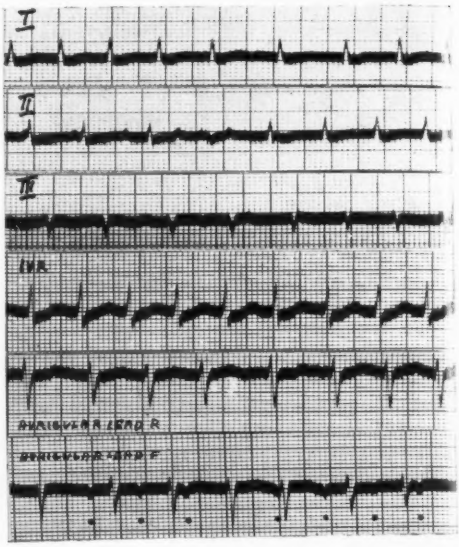


FIG. 4.—Case 4. A-V dissociation with high auricular and ventricular rates. Discussed in text. Distinct P waves are only seen in lead II and in auricular lead F.

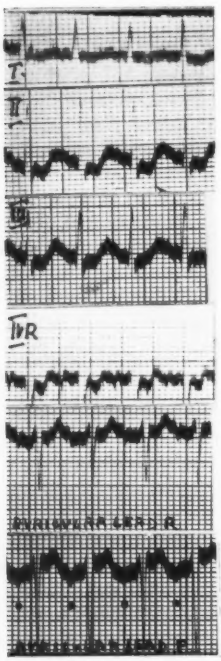


FIG. 5.—Case 5. Supraventricular tachycardia. Rate 170 a minute. Inverted P waves in auricular lead F.

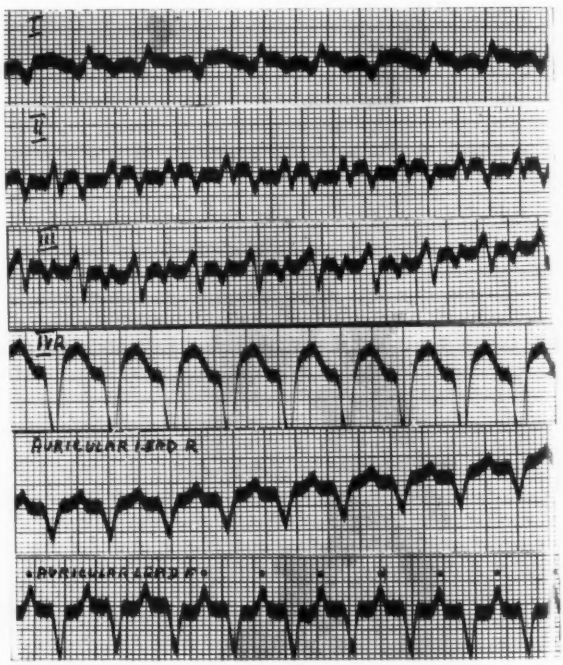


FIG. 6.—Case 6. Acute coronary artery occlusion. Tracing discussed in text. P waves are probably superimposed on T waves in auricular lead F. See also Fig. 7.

but no cardiac enlargement and no gross myocardial fibrosis; there were extensive pleural adhesions on the left side and partial collapse of the left lung. The patient was very restless, making it impossible to get a steady record. It shows supraventricular tachycardia. Though the tracing is technically unsatisfactory, auricular lead F shows the most distinct P waves. They are inverted, at a rate of about 170 a minute, and can be clearly differentiated from the preceding T waves. Auricular lead R shows diphasic P waves at the same rate.

The cardiograms shown in Fig. 6 and 7 are those of a man, aged 67 years, who was admitted with occlusion of the coronary artery and paroxysmal tachycardia. The tracings are diagnostic of anterior myocardial infarction. Fig. 6 shows probably auricular tachycardia at a rate of 160 a minute. The P waves in auricular lead F are, we think, superimposed on the T waves and probably this is the case in the other leads also. On the other hand, it is difficult to exclude flutter at the rate of 320 with a 2 : 1 response on this tracing alone. Fig. 7A, taken six days later after digitalization, shows auricular tachycardia at a rate of 150 a minute, with a 2 : 1 A-V block in the limb leads and Luciani-Wenckebach periods

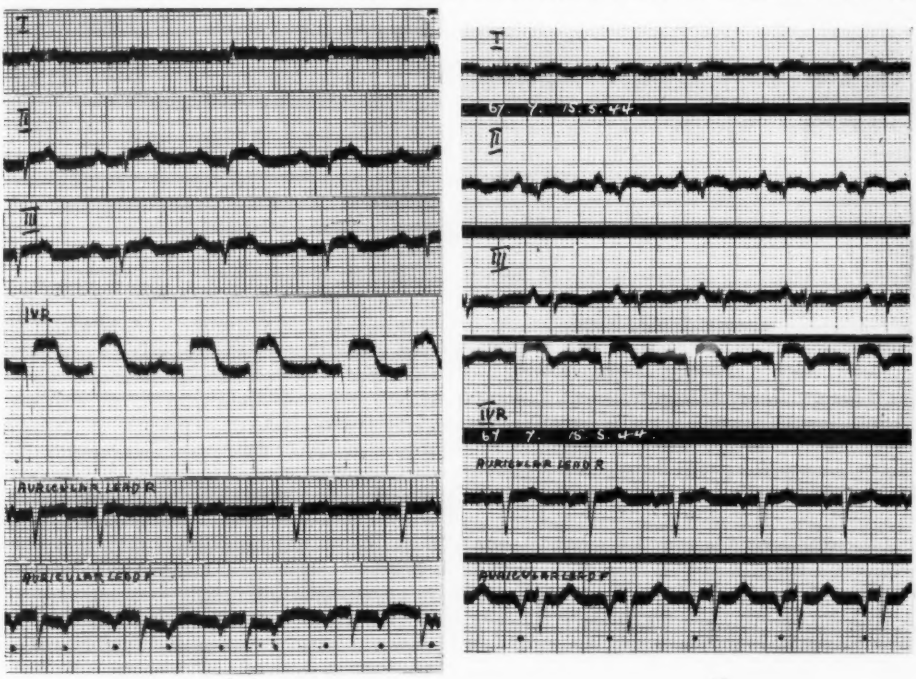


FIG. 7.—Case 6 (A). After digitalization. Auricular tachycardia at the rate of 150 a minute, with 2 : 1 A-V block in the limb leads and Luciani-Wenckebach periods at times in the chest leads. Inverted P waves in auricular lead F.

(B). After discontinuation of digitalis for 23 days. Sinus rhythm with normal P–R interval. Here again, inverted P waves in auricular lead F.

at times in the chest leads. Auricular lead F shows conspicuous inverted P waves. Fig. 7B, taken 23 days after discontinuation of digitalis, shows sinus rhythm with normal P–R interval, and auricular lead F shows deeply inverted P waves.

AURICULAR FLUTTER AND FIBRILLATION

Only one case of undoubted flutter was studied. The cardiogram of this patient, a man, aged 35 years, with mitral stenosis, is reproduced in Fig. 8 (page 245). It shows a 2 : 1 auricular flutter with marked flutter waves in auricular lead F.

Seven cases of auricular fibrillation were studied. In three of them the fibrillation waves were more conspicuous in the auricular leads than in the standard leads, while in the remaining four there was no appreciable difference.

Sinus Rhythm

In addition to the cases of paroxysmal tachycardia in which tracings showing sinus rhythm were obtained after the paroxysm had stopped, 50 cases were available for study, and 60 cardiograms were taken. All but three were obtained from patients suffering from various forms of heart disease. It is not suggested that the auricular leads have any significant advantages over the standard leads in cases of normal auricular rhythm: nevertheless, a brief description of the form and amplitude of the P wave in the auricular leads may be of interest. Of the 60 cardiograms 15 included both auricular leads R and F. In the remaining 45 only auricular lead F was recorded. The P wave in auricular lead R was positive in 10, and diphasic in 5 instances. Only in one instance was the P wave in auricular lead R greater in amplitude than in auricular lead F; in another both leads showed equal P waves; and in 13 instances auricular lead F showed more conspicuous P waves than auricular lead R. A comparison of auricular lead R with the standard leads revealed only one case in which the largest P waves occurred in auricular lead R. In the remainder, at least one of the standard leads showed P waves either equal in amplitude to those in auricular lead R or even larger. The P wave in auricular lead F was upright in 3, diphasic in 6, and inverted in 51 instances. Auricular lead F was compared with the standard lead showing the largest P wave; and it was found that, judged by the amplitude of this wave, auricular lead F was superior to the standard lead in 19, equal to it in 16, and inferior in 25 instances.

Discussion

The special chest leads used in this study often display larger auricular waves than the standard leads, and thus help the interpretation of records showing abnormal rhythms. Auricular lead F appears to be superior to auricular lead R. Though Wood and Selzer (1939) stated that the right arm was the better distal electrode for the study of auricular activity, it is open to question whether their results can be directly compared with ours because they used a different technique, placing the exploring electrode in the fourth intercostal space at the right sternal border (leads CR_1 and CF_1). In ten unselected cases we studied the P waves in both auricular leads R and F, and in leads CR_1 and CF_1; the comparative figures are shown in Table I. The amplitude of the P wave was measured in the four leads to the nearest 0·5 mm. from the top of the isoelectric line in upright waves and from the bottom in inverted waves. Though the number of cases is far too small to draw conclusions, it appears that auricular lead F is not only superior to auricular lead R, but is also the best of the four leads for the study

TABLE I.—Size of P Waves in Various Leads

Case Number	Rhythm	Amplitude of P wave in mm. in			
		Auric. lead R	Auric. lead F	CR_1	CF_1
1 (Fig. 8)	Aricular flutter	1·5	3	1·5	2
2	2 : 1 A-V block	2·5	2·5	2·5	2·5
3	Sinus rhythm	1	2	1	2
4	Auricular fibrillation	1	2	1	1·5
5	Sinus rhythm	2·5	1	2	1
6	Sinus rhythm	2	2·5	2	2·5
7	Auricular fibrillation	1	2	1	2
8 (Fig. 9)	Sinus rhythm	1·5	4	4	2
9	Auricular fibrillation	1	1	1	1
10	Sinus rhythm	1	1	2	1
	Mean amplitude	1·5	2·1	1·8	1·75

of auricular activity. On the other hand, if the exploring electrode is placed in the fourth intercostal space at the right sternal border, the results are likely to be better when the exploring electrode is paired with the right arm than when paired with the left leg. An illustrative example is shown in Fig. 9. The cardiogram was obtained from a man aged 45 years, suffering

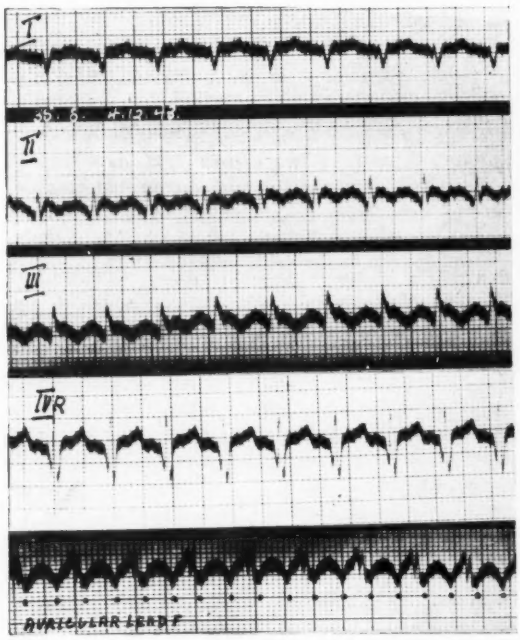


FIG. 8.—Case 7. Mitral stenosis, with 2 : 1 auricular flutter. Conspicuous flutter waves in auricular lead F.

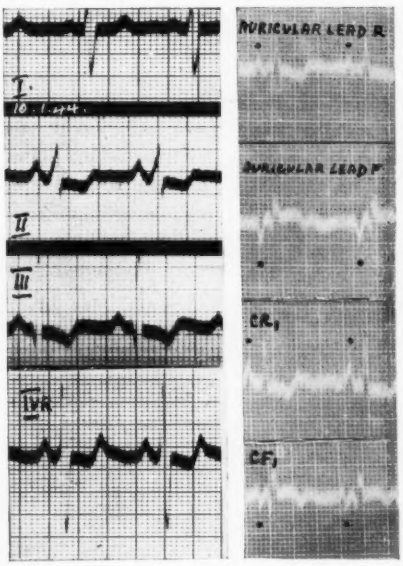


FIG. 9.—Case 8. Chronic cor pulmonale. Large auricular deflections in auricular lead F, and in lead CR_1.

from chronic cor pulmonale. The tracing shows equally large P waves in auricular lead F and in lead CR_1 (inverted in the former, upright in the latter), and much smaller P waves in auricular lead R and in lead CF_1. Another advantage of auricular lead F over lead CR_1 is that the P wave in the former is nearly invariably opposite in direction to that in lead II. Thus, a combined analysis of these two leads is more likely than any of the standard leads to disclose a P wave obscured by the ventricular complex, and especially by the T wave, combining to simulate a split T wave. The practical value of this can be seen in the tracings reproduced in Fig. 1A and 5.

In many records the auricular leads failed to display larger P waves than did the standard leads. It is not easy to explain this lack of uniformity. It would seem at first that the size of the right auricle is an important factor determining the amplitude of the P wave. Lewis (1910), in fact, found that the maximal oscillations occurred in cases of auricular fibrillation in which the right auricle was enlarged. On the other hand, Evans (1941) found that conspicuous auricular waves in lead CR_1 were by no means dependent on extension of the heart to the right. Our results agree with those of Evans. We were unable to find any close correlation between the size of the right auricle and the amplitude of the P waves in the auricular leads. Out of the six cases of paroxysmal tachycardia with distinct P waves in the auricular leads, four were examined radioscopically: in none was the right auricle seen to be enlarged; in two all cardiac chambers were normal in size; the third (coronary thrombosis) had moderate enlargement of the left ventricle; and the fourth (mitral stenosis) showed slight enlargement

of both ventricles and of the left auricle. The fifth case of paroxysmal tachycardia was too ill to be taken to the screening room; he died shortly after admission, and the autopsy revealed no cardiac enlargement. In the sixth case, there were no data available regarding the size of the heart apart from physical examination, which did not suggest cardiac enlargement. The four remaining cases of paroxysmal tachycardia with doubtful or unsuccessful auricular leads also had normal-sized right auricles: in one the heart was normal in size; in two there was slight enlargement of the left ventricle; in the fourth, which was not screened, autopsy showed only slight enlargement of the left ventricle. The patient with mitral stenosis and auricular flutter, whose cardiogram is reproduced in Fig. 8, was proved by radioscopy to have a general cardiac enlargement, including possible dilatation of the right auricle. In the cases of auricular fibrillation and sinus rhythm there was also a lack of correlation between the amplitude of the P wave and the size of the right auricle. It is noteworthy that in a case of mitral stenosis and auricular fibrillation with very marked enlargement of both auricles, confirmed by autopsy, the oscillations were hardly visible. On the other hand, a comparatively large P wave (3 mm. in amplitude) was encountered in a case of coronary thrombosis (T III type) in which the autopsy showed no auricular enlargement at all. It is evident from this analysis that the size of the right auricle cannot be the only factor determining the amplitude of the P wave. The anatomical position of the right auricle in the thoracic cavity and its relation to the anterior chest wall are possibly important factors influencing the amplitude of the P wave in the auricular leads; but at present we have no confirmatory evidence in support of this suggestion.

Summary

Special chest leads were used for the study of auricular activity and compared with the standard leads. The exploring electrode was placed in the third intercostal space at the right sternal border and paired with the right arm or left leg. The former lead was referred to as auricular lead R, the latter as auricular lead F. Auricular lead F was found to be more useful than auricular lead R.

These special chest leads were studied in cases with paroxysmal tachycardia, with auricular fibrillation and flutter, and in a number with sinus rhythm. They showed auricular waves often to much better advantage than did the standard leads. It is suggested, therefore, that the recording of these leads is indicated in all cases in which there is doubt about the activity of the auricles.

No correlation was found between the size of the right auricle and the amplitude of the P wave as recorded in the auricular leads. It seems, therefore, that the amplitude of the P wave in the auricular leads is also determined by factors other than the size of the right auricle. The anatomical position of the right auricle in the thoracic cavity and its relation to the anterior chest wall are suggested as possible factors.

I am indebted to Professor Hume for his helpful criticism and advice. I wish to thank Dr. Maurice Campbell and Dr. William Evans for their suggestions, and Dr. I. E. McCracken, Medical Officer of Health, Newcastle on Tyne, and Dr. G. P. Harlan, Medical Superintendent, Newcastle General Hospital, for facilities provided.

References

Barker, P. S., Wilson, F. N., Johnston, F. D., and Wishart, S. W. (1943). *Amer. Heart J.*, **25**, 765.
Brown, W. H. (1936). *Ibid.*, **12**, 307.
Deglaude, L., and Laubry, P. (1939). *Arch. Mal. Cœur*, **32**, 121.
Drury, A. N., and Iliescu, C. C. (1928). *Heart*, **8**, 171.
Evans, W. (1941). *Brit. Heart J.*, **3**, 247.
Faulkner, J. M. (1943). Quoted by Williams and Ellis.
Holzman, M. (1937). *Arch. f. Kreislauff.*, **1**, 1.
Lewis, T. (1910). *Heart*, **1**, 306.
Lian, C., and Pinchenzon, B. (1938). *Cardiologia*, **2**, 56.
Schoenewald, G. (1939). *Middl. Hosp. J.*, **39**, 183.
Standardization of Præcordial Leads. Memorandum by the Cardiac Society of Great Britain and Ireland and the American Heart Association (1939). *Brit. Heart J.*, **1**, 43.
Williams, C., and Ellis, L. B. (1943). *Arch. intern. Med.*, **71**, 137.
Wood, P., and Selzer, A. (1939). *Brit. Heart J.*, **1**, 49.

PROCEEDINGS OF THE CARDIAC SOCIETY OF GREAT BRITAIN AND IRELAND

The EIGHTH ANNUAL GENERAL MEETING of the Cardiac Society of Great Britain and Ireland was arranged to be held at University College Hospital Medical School, London, on Thursday, July 20, 1944, under the Chairmanship of SIR THOMAS LEWIS, F.R.S.

Early in July a majority of the Council decided reluctantly that this meeting should not be held.

PRIVATE BUSINESS

The following private business was conducted by postal vote with the written approval of 23 ordinary members, no members objecting.

1. The minutes of the last meeting were printed in the Journal (5, 238, 1943).

2. The accounts, held over for audit and approval, showed a balance of £40 7*s*. 5*d*. The Council had decided that no subscription should be collected for the year 1944/45.

3. The Secretary, on the recommendation of the Council, was re-appointed for another year and William Evans was again asked to act as Assistant Secretary.

4. Four Ordinary Members were elected as *Extra-Ordinary Members*.

A. G. Gibson	W. E. Hume
Donald Hall	H. J. Starling

5. The following new Members were elected:—

Ordinary Members	*Associate Members*
Janet Aitken	D. R. Cameron
Doris Baker	J. R. B. Hern

Six Associate Members were re-elected for another period of three years.

6. Subsequently, by postal vote, A. A. F. Peel, Glasgow, and B. T. Parsons-Smith, London, were elected members of the Council for the years 1944–48.

7. The Secretary reports the following events and decisions of the Council as he was unable to bring them before the Meeting.

(*a*) He had written on behalf of the Society to the relatives of Frederick John Poynton, Honorary Member, whose obituary notice had been published in the Journal (6, 96, 1944).

(*b*) In accordance with the decision of the last General Meeting, the Secretary had approached the British Pædiatric Association, who had agreed that their Committee and the Committee of the Cardiac Society should meet together to try and draw up a combined report on The Care of Rheumatic Children. The draft report was produced later in the year and certain modifications were made in this by the Executive of the B.P.A. The Council of the Cardiac Society at its meeting on March 22, 1944, discussed this report and asked the Chairman, Sir Maurice Cassidy, and the Secretary, Maurice Campbell, to accept the invitation to attend the meeting of the Executive of the British Pædiatric Association, with authority to propose and accept minor changes within certain limits discussed by the Council. The Chairman and Secretary attended this meeting on March 25, 1944, and agreement was reached to publish the document as a joint report by the Cardiac Society and the British Pædiatric Association. *British Heart Journal* (1944), 6, 99.

(*c*) The Royal College of Physicians had asked the Cardiac Society to appoint a member to serve on the Committee for the revision of the Nomenclature of Diseases and the Council had appointed Maurice Campbell. Subsequently the R.C.P. Committee asked the Cardiac Society to appoint two members to help with the revision of the

section on Diseases of the Circulatory System, and the Secretary with the approval of the Chairman submitted the names of John Parkinson and Maurice Campbell.

(*d*) The Memorandum on Rehabilitation of Cardiac Patients was further considered by the Council, and with further modifications was approved for publication at the Council Meeting on March 22, 1944. The Secretary was instructed to send it for publication to the *British Medical Journal* (April 22, 1944) and to the *Lancet*. It is reprinted below.

Public Business

The proposed programme of Public Business was as follows:—

Discussion

Diseases of the Pericardium

Opened by Terence East, Bruce Perry, John Parkinson, and Tudor Edwards

Demonstrations

Specimens of Normal and Pathological A-V Conduction

Sir Thomas Lewis

A Case of Aortic Aneurysm, successfully Wired

Geoffrey Bourne

Short Communications

A Case of Tuberculous Pericarditis

Leslie Cole

(Published in full; p. 185)

The Action of Intravenous Digoxin

J. McMichael and E. V. Sharpey-Schafer

Electrocardiograms of a Dying Heart after Coronary Thrombosis

T. F. Cotton

Cardiac Enlargement with Bradycardia in Recruits

Crighton Bramwell

Cardiac Enlargement in Anæmia

Alastair Hunter

The Nature of Paroxysmal Tachycardia

William Evans

(Published in full; p. 221)

Surgical Treatment of Patent Ductus Arteriosus

Rae Gilchrist

(To be published in full; 7, p. 1, 1945)

Two Cases of Malignant Hypertension treated by Unilateral Nephrectomy

C. Bruce Perry

Nomenclature of Cardiac Disease

Maurice Campbell

Rehabilitation of Cardiac Patients

Many patients, those with fractures, for example, derive great help from efficient rehabilitation. Without it they may be handicapped for long periods; with it most of them may be enabled to undertake full activities and to resume their normal work. The success achieved in this direction has led to the suggestion that similar methods should be used more widely, and the Council of the Cardiac Society felt the time was opportune for expressing their views and bringing forward some questions for wider discussion.

Patients with heart disease are in rather a special category as regards rehabilitation. In the first place any activity, including walking or other forms of physical effort, must automatically increase the work done by the heart. If the patient is going to recover completely, e.g. after some temporary infection, cardiac recovery will often proceed *pari passu* with recovery from the infection and no more than simple graduated exercises may be needed to ensure it; in fact he may need limiting rather than encouraging in his rate of progress. In other cases complete recovery may be impossible, and it may be most important that he should not return to his previous work and activity.

Further, the correct diagnosis of the condition of the heart and especially of the heart muscle, and the correct assessment of the cardiac reserve are of fundamental importance, and harm may be done by too much or by too little activity at any particular stage.

In our opinion there is only limited scope for rehabilitation, as the term is now being employed, for patients suffering from organic cardiovascular disease. Physiotherapy and graduated exercise are, of course, useful, but must be supervized by a doctor with special knowledge of heart disease. The main problem is the decision as to how much general activity should be allowed, and this depends more on the success of the doctor in charge in diagnosis and assessment of the patient's cardiac reserve than on the availability of skilled assistants in physiotherapy or occupational therapy. The need for suitable convalescent homes is, of course, generally accepted.

There are, however, cases in which the heart is temporarily under suspicion, which fuller investigation proves to be unjustified, e.g. systolic murmurs which the inexperienced may hesitate to disregard but the experienced are able to label as "insignificant." In many such cases all that is necessary is for an authoritative opinion that the heart is normal and that the patient is, therefore, capable of leading a full active life, but in others rehabilitation may be needed. There is also scope for rehabilitation in the case of effort syndrome, which is at least as common in civil life as under service conditions, though here it may appear diagnozed as "cardiac anxiety state," "traumatic neurasthenia" or "post-influenzal tachycardia." But we suggest that the rehabilitation of these patients, whether by graduated exercises or by simple psychotherapy, should not be carried out at cardiac clinics, once it has been decided that there is no organic disease.

We suggest, therefore, that there should be more well-staffed and well-equipped out-patient cardiac clinics at general hospitals, preferably under the care of an experienced cardiologist. Here a correct diagnosis could be made, and the patient could be advised about suitable employment and be kept under observation when engaged in such employment. The help of the Almoner's department would often be useful. If necessary the patients could receive specialized treatment that experience has shown to be more satisfactory in cardiac clinics, such as the treatment of auricular fibrillation with digitalis or of congestive failure with mercurial diuretics, or the control of symptoms of early angina.

Special difficulties may arise in finding suitable work for patients with some permanent limitation as a result of heart disease, and this is a problem that should be discussed. Many such persons, especially the younger ones with rheumatic heart disease, are precluded from those occupations which are most appropriate to their condition, e.g. Civil Service, Banking, and Insurance. They are, therefore, forced to take less suitable work for which no medical examination is necessary and in which their health may break down. Alternatively, they are out of employment and the nation is losing citizens who might give valuable service for a considerable number of years.

We recommend that where a patient is fit for particular work his acceptance should not be impossible because he has valvular disease which precludes his joining an ordinary life assurance scheme; it should be possible to make special arrangements for accepting such patients in some branches of the Civil Service, Banking, etc.

Another difficulty is with the older patient who is beginning to be incapacitated by early signs of failure or angina or by such lesions as hypertension, arteriosclerosis, or myocardial disease which may lead to failure if his previous employment is no longer suitable. Such a patient would often be

better at work and would like to be at work, but cannot find anything because he is not fit for the heavy work that he did before.

We recommend that there should be some industrial advisory board or government department, through which arrangements could be made to ensure that these partially disabled patients could obtain suitable work, after, when necessary, appropriate special training. Often this would not be necessary and the patients' previous employers might be able to carry out the medical recommendations, especially if they were safeguarded against claims against them under the Employers' Liability Act,* in the event of a breakdown of an employee known to be suffering from heart disease.

The special care of rheumatic children is being dealt with elsewhere in a separate memorandum.

MAURICE CASSIDY,
Chairman.

MAURICE CAMPBELL,
Secretary.

Cardiac Society of Great Britain and Ireland.

* It has been pointed out that the Workman's Compensation Act should be referred to here.

INDEX OF AUTHORS

A

Arriens, R. T. H. (and I. Pines and A. Sanabria): Mercurial diuretics: The addition of magnesium sulphate to prevent toxic effects. 197.

B

Bain, C. W. Curtis: Incomplete bundle branch block. 139.
Barrett, A. M. (and Leslie Cole): A case of tuberculous pericarditis. 185.
Bramwell, Crighton (and A. Morgan Jones): Acute left auricular failure. 129.
Braun, K. (and L. E. Schindel): The place of foliandrin within the group of cardiac glucosides. 149.
Brown, James W. (and Frank Hampson): Temporal arteritis. 154.

C

Campbell, Maurice: Complete heart block. 69.
——: Frederick John Poynton. 96.
Cole, Leslie (and A. M. Barrett): A case of tuberculous pericarditis. 185.

D

Daniel, G. H.: Social and economic conditions and the incidence of rheumatic heart disease. 103.
Dawson, G. D. (and A. Morgan Jones) : Synchronous heart sound recording. 48.
Duras, Paul F.: Heart block with aneurysm of the aortic sinus. 61.

E

Evans, William: The heart in myotonia atrophica. 41.
——: The unity of paroxysmal tachycardia and auricular flutter. 221.

F

Forbes, G. W. (and J. S. Lawrence): Paroxysmal heart block and ventricular standstill. 53.

H

Hampson, Frank (and James W. Brown): Temporal arteritis. 154.
Holford, J. M.: Unusual electrocardiogram in dextrocardia. 105.
Howell, Trevor H.: Heart failure in the aged. 20.
Hume, William E. (and P. Szekely): Cardiac involvement in spirochaetal jaundice. 135.

J

Jones, A. Morgan (and Crighton Bramwell): Acute left auricular failure. 129.
—— (and G. D. Dawson): Synchronous heart sound recording. 48.

K

Katz, L. N. (R. Langendorf, and A. J. Simon): Reciprocal beating initiated by ventricular premature systoles. 13.

L

Langendorf, R. (L. N. Katz, and A. J. Simon): Reciprocal beating initiated by ventricular premature systoles. 13.
Lawrence, J. S. (and G. W. Forbes): Paroxysmal heart block and ventricular standstill. 53.
Lewes, David: Pulmonary embolism: The clinical and cardiographic progress of a case. 161.
Lowe, T. E. (and W. B. Wartman): Myocardial infarction. 115 and 183.

M

Mackeith, Ronald: Adrenal-sympathetic syndrome. 1.
Macleod, Alastair: Cardio-aortic fistula. 194.
McMichael, John (and E. P. Sharpey-Schafer): Cardiac output in man by a direct Fick method. 33.
Miller, R.: Auriculo-ventricular rhythm. 107.

P

Pines, Ignacy (and A. Sanabria and R. T. H. Arriens): Mercurial diuretics: The addition of magnesium sulphate to prevent toxic effects. 197.
Prescott, Frederick: Clinical evaluation of the pressor activity of methedrine, neo-synephrine, paredrine, and pholedrine. 214.

S

Sanabria, A. (and I. Pines and R. T. H. Arriens): Mercurial diuretic: The addition of magnesium sulphate to prevent toxic effects. 197.
Saracoglu, K.: A rare case of heart block. 93.
Schindel, L. E. (and K. Braun): The place of foliandrin within the group of cardiac glucosides. 149.
Schott, A.: Circulatory failure due to vitamin B deficiency. 27.
Sharpey-Schafer, E. P. (and John McMichael): Cardiac output in man by a direct Fick method. 39.
Simon, A. J. (R. Langendorf, and L. N. Katz): Reciprocal beating initiated by ventricular premature systoles. 13.
Smirk, F. H.: Casual and basal blood pressures. IV. Their relationship to the supplement pressure with a note on statistical implications. 176.
Stern, V. S.: Stokes-Adams attacks in a child. 66.
Stokes, Wilfred: Nicotinic acid in the treatment of angina pectoris. 157.
Sunderland, Sydney (and R. J. Wright-Smith): Congenital pericardial defects. 167.
Szekely, P. (and William E. Hume): Cardiac involvement in spirochætal jaundice. 135.
——, Chest leads for the demonstration of auricular activity. 238.

T

Thompson, R. B.: Myxoma of the left auricle. 23.

W

Wartman, W. B. (and T. E. Lowe): Myocardial infarction. 115 and 183.
Wood, Anne M.: Perforation of the interventricular septum due to cardiac infarction. 191.
Wright-Smith, R. J. (and S. Sunderland): Congenital pericardial defects. 167.

INDEX OF SUBJECTS

A

Acute left auricular failure (Crighton Bramwell and A. Morgan Jones). 129
Adrenal-sympathetic syndrome (Ronald Mackeith). 1.
Aneurysm of aortic sinus, heart block with (P. F. Durac). 61.
Angina pectoris, nicotinic acid in the treatment of (Wilfred Stokes). 157.
Aortic sinus, aneurysm of, with heart block (P. F. Duras). 61.
Arteritis, temporal (James W. Brown and F. Hampson). 154.
Auricular failure, acute left (Crighton Bramwell and A. Morgan Jones). 129.
Auricular flutter and paroxysmal tachycardia, the unity of (William Evans). 221.
Auriculo-ventricular rhythm (R. Miller). 107.

B

British Paedratric Association: Report on the care of rheumatic children. 99.
Bundle branch block, incomplete (C. W. Curtis Bain). 139.

C

Cardiac involvement in spirochaetal jaundice (William E. Hume). 135.
Cardiac output in man by a direct Fick method (John McMicheal and E. P. Sharpey-Schafer). 33.
Cardiac Society of Great Britain and Ireland, Proceedings of. 247.
Cardiac Society: Report on the care of rheumatic children. 99.
Cardio-aortic fistula (Alastair Macleod). 194.
Casual and basal blood pressures. IV. Their relationship to the supplemental pressure with a note on statistical implications (F. H. Smirk). 176.
Chest leads for the demonstration of auricular activity (P. Szekely). 238.
Circulatory failure due to vitamin B deficiency (A. Schott). 27.
Clinical evaluation of the pressor activity of methedrine, neo-synephrine, paredrine, and pholedrine (Frederick Prescott). 214.
Complete heart block (Maurice Campbell). 69.
Congenital pericardial defects (Sydney Sunderland and R. J. Wright-Smith). 167.

D

Dextrocardia, unusual electrocardiogram in (J. M. Holford). 105.

E

Embolism, pulmonary, the progress of a case (David Lewes). 161.

F

Foliandrin, the place of, within the group of cardiac glucosides (L. E. Schindel and K. Braun). 149.

H

Heart block with aneurysm of the aortic sinus (Paul F. Duras). 61.
Heart block, complete (Maurice Campbell). 69.
Heart block, a rare case of (K. Saracoglu). 93.
Heart block, paroxysmal, and ventricular standstill (J. S. Lawrence and G. W. Forbes). 53.
Heart failure in the aged (Trevor Howell). 20.
Heart in myotonia atrophica (William Evans). 41.
Heart sound recording, synchronous (G. D. Dawson and A. Morgan Jones). 48.

I

Incomplete bundle branch block (C. W. Curtis Bain). 139.
Infarction, myocardial (T. E. Lowe and W. B. Wartman). 115 and 183.

J

Jaundice, cardiac involvement in spirochaetal (W. E. Hume and P. Szekely). 135.

M

Mercurial diuretics: the addition of magnesium sulphate to prevent the toxic effects of their intravenous administration (Ignacy Pines, Antonio Sanabria, and R. T. Hernandez Arriens. 197
Myocardial infarction (T. E. Lowe and W. B. Wartman). 115 and 183.
Myotonia atrophica, the heart in (William Evans). 41.
Myxoma of the left auricle (R. B. Thompson). 23.

N

Nicotinic acid in the treatment of angina pectoris (Wilfred Stokes). 157.
Nodal (auriculo-ventricular) rhythm (R. Miller). 107.

O

Old age, heart failure in (T. H. Howell). 20.

P

Paroxysmal heart block and ventricular standstill (J. S. Lawrence and G. W. Forbes). 53.
Paroxysmal tachycardia and auricular flutter, the unity of (William Evans). 221.
Perforation of the interventricular septum due to cardiac infarction (Anne M. Wood). 191.
Pericarditis, tuberculous (A. M. Barrett and Leslie Cole). 185.
Poynton, Frederick John (Maurice Campbell). 96.
Proceedings of the Cardiac Society of Great Britain and Ireland. 247.
Pulmonary embolism: The clinical and cardiographic progerss of a case (David Lewes). 161.

R

Reciprocal beating initiated by ventricular premature systoles (R. Langendorf, L. N. Katz, and A. J. Simon). 13.
Report : The care of rheumatic children. 99.
Rheumatic children, the care of (Report). 99.
Rheumatic heart disease, social and economic conditions and the incidence of (G. H. Daniel). 103.

S

Social and economic conditions and the incidence of rheumatic heart (G. H. Daniel). 103.
Stokes-Adams attacks in a child (V. S. Stern). 66.
Synchronous heart sound recording (G. D. Dawson and A. Morgan Jones). 48.

T

Temporal arteritis (James W. Brown and Frank Hampson). 154.
The care of rheumatic children (Report). 99.
The unity of paroxysmal tachycardia and auricular flutter (William Evans). 221.
Tuberculous pericarditis (A. M. Barrett and Leslie Cole). 185.

U

Unusual electrocardiogram in dextrocardia (J. M. Holford). 105.

V

Ventricular standstill and paroxysmal heart block (J. S. Lawrence and G. W. Forbes). 53.
Vitamin B deficiency, circulatory failure due to (A. Schott). 27.

PRINTED IN GREAT BRITAIN BY WILLIAM CLOWES AND SONS, LIMITED, LONDON AND BECCLES.